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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, December 23, 2009 1:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Abhik Das; Wally Carlo; Gantz, Marie
Subject: Re: SUPPORT Analyses

Hi Rose
Obviously we did not do a good job in defining when and how to define Oxygen dependency and what oximeter to use. I believe that the results are still OK as the majority used conventional oximeters and I believe that any bias would have been balanced for those that used study oximeters.
If we were reporting a significant difference then we would need to be more concerned - as things stand I doubt that the direction of change would be changed. We can do analyses comparing BPD using both definitions comparing the site practices - ie compare the 11 sites using a conventional oximeter with the remaining ones and see if there is any major difference The majority did as we intended - they used clinical oximeters for both.
All the best for the Holidays
Neil

On 12/23/09 6:52 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> Here are the results from the oximeter questions - Iowa answer is
> mixed depending on the location of the infant. There were 3 sites
> that challenged using the study oximeter according to these results.
> Perhaps we should look at the Phys def forms and see if the sites
> recorded Masimo on the form (as we asked which oximeter was used for the challenge.
>
> For the BPD def - we could look at the individual cases to see exactly
> how much oxygen the children were on.
>
> Let me know what you think
>
> Rose
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, December 22, 2009 11:51 AM
> To: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Wally
> Carlo; Gantz, Marie
> Subject: Re: SUPPORT Analyses
>
> Hello Everyone
> My email sent this out apparently yesterday - I apologize as I did not
> resend this.
> I think my email is having seizures or a virus I am sorry for any
> inconvenience Please ignore it as I already sent this out you Be well
> and all the best for the Holidays and New Year Neil
>
>

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> On 12/22/09 8:42 AM, "Wade Rich" <wrich@ucsd.edu> wrote:
>
>
>
>
> From: Finer, Neil
> Sent: Monday, December 21, 2009 12:57 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wally Carlo;
> Rich, Wade; Abhik Das
> Subject: SUPPORT Analyses
>
> Hello Everyone
> I would now like to have more analyses for the SpO2 study. I want to
> see the actual FiO2 requirements for the infants during the first 2 weeks, and later.
> We can do a survival type analysis and I will leave that to Marie to
> figure out The study was designed to separate the infants by oxygen
> exposure and now we need to know how well we achieved this with the
> study POs.
> In addition we need to start looking at the actual durations of SpO2 <
> 80 and
> > 96% as well as durations below 75%, < 70%, <60 and < 50% as
> > durations
> comparing low and hi groups.
> We may want these to respond to any questions form reviewers Thanks
> Marie for running these.
> Be well
> Neil
>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"; "Rich, Wade"; "Abhik Das"; "Wally Carlo"; "Gantz, Marie"
Subject: RE: SUPPORT Analyses
Date: Wednesday, December 23, 2009 9:52:00 AM
Attachments: Oximeter.xls

Here are the results from the oximeter questions - Iowa answer is mixed depending on the location of the infant. There were 3 sites that challenged using the study oximeter according to these results. Perhaps we should look at the Phys def forms and see if the sites recorded Masimo on the form (as we asked which oximeter was used for the challenge.

For the BPD def - we could look at the individual cases to see exactly how much oxygen the children were on.

Let me know what you think

Rose

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 22, 2009 11:51 AM
To: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Wally Carlo; Gantz, Marie
Subject: Re: SUPPORT Analyses

Hello Everyone
My email sent this out apparently yesterday -
I apologize as I did not resend this.
I think my email is having seizures or a virus
I am sorry for any inconvenience
Please ignore it as I already sent this out you
Be well and all the best for the Holidays and New Year
Neil

On 12/22/09 8:42 AM, "Wade Rich" <wrich@ucsd.edu> wrote:

From: Finer, Neil
Sent: Monday, December 21, 2009 12:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wally Carlo; Rich, Wade; Abhik Das
Subject: SUPPORT Analyses

Hello Everyone
I would now like to have more analyses for the SpO2 study. I want to see the actual FiO2 requirements for the infants during the first 2 weeks, and later. We can do a survival type analysis and I will leave that to Marie to figure out
The study was designed to separate the infants by oxygen exposure and now we need to know how well we achieved this with the study POs.
In addition we need to start looking at the actual durations of SpO2 < 80 and > 96% as well as durations below 75%, < 70%, <60 and < 50% as durations comparing low and hi groups.
We may want these to respond to any questions form reviewers
Thanks Marie for running these.
Be well
Neil

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	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	RTI	NICHD	Chairman	Total
SUPPORT | Oximeters used for Physiologic Def. Challenge																				
Voted	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V				15
For determination of eligibility for the challenge, did you determine eligibility using:																				
Study oximeter										1	1	1			1	1				5
Clinical	1	1	1	1	1	1	1		1				1		1					10
Brown	Per FiO2 documentation in medical record at 36 weeks.																			
If a challenge occurred, did your site use:																				
Study Oximeter												1			1	1				3
Clinical	1	1	1	1	1	1	1	1	1	1	1		1		1					13
For BPD by oxygen definition, did you use:																				
Study oximeter										1	1	1			1	1				5
Clinical	1	1	1	1	1	1	1	1	1				1		1					11
Utah	Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and																			
Indiana	We followed the manual guidelines for use of the study oximeters – so any baby on oxygen indeed was still on a study oximeter up until 36 weeks. We determined if babies were eligible for a challenge at 36 weeks –																			
Alabama	At UAB, determination of eligibility by study pulse oximeter used on 36 week PCA day. If infant had challenge done, it was done with a clinical pulse oximeter. Study PO left on baby on day 36 week because 4 data																			
Dallas	I looked at the completed PHY02BASE forms for our SUPPORT babies who had challenges. According to my records one of our infants was tested with a Masimo (not sure why or how it happened). All of the other																			
UNM	In New Mexico the Study oximeter was kept on the patient until 36 weeks, death, transfer, or room air. Therefore, the study oximeter was used to determine eligibility for RA challenge, and to record the use of oxygen																			
Emory	I went back through our SUPPORT folders and I think that only (b) and (b) were evaluated for BPD using the study monitors. Both coded as not eligible for reduction because sats too low. I think these are																			
Duke	The study oximeter was used to determine eligibility for the challenge (for those that were still on the study oximeter at 36 weeks) and was also used for the challenge.																			
IOWA	Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and others on the clinical one. If you need me to se																			

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "srhintz@stanford.edu"
Subject: Re: the analyses thus far
Date: Tuesday, December 22, 2009 7:24:42 PM

So sorry to hear about (b) (6)
I will be in tomorrow and thursday

Take care
Rose

----- Original Message -----
From: Susan Hintz <srhintz@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Dec 22 13:01:00 2009
Subject: RE: the analyses thus far

Oh yes. It is just that all all the administrative staff is not working. So - the phones roll over to voice mail at our office. You can always reach me by cell.

Hey, did I tell you (b) (6) Oh my heavens.

Susan

>Are you working this week???
>
>-----Original Message-----
>From: Susan Hintz [mailto:srhintz@stanford.edu]
>Sent: Tuesday, December 22, 2009 12:14 PM
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Subject: Re: the analyses thus far
>
>Hi Rose
>
>I am waiting to hear back from Qing. I suspect she is out of the
>office, but she did tell me she would definitely be around during the
>week of the 28th. At least I am glad you agree I am not going crazy,
>and the numbers don't seem to make sense. I am sure we will get it
>sorted out, I am just anxious to move along so we can have something
>for late breaker.
>
>I hope you have a great Christmas, and that the storm doesn't continue
>to disrupt things too much for you!
>
>Susan
>
>Sent from my iPhone
>
>On Dec 22, 2009, at 5:50 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
><higginsr@mail.nih.gov
> > wrote:
>
>> I agree - the numbers don't make sense
>> Was each reading counted twice for each individual infant?

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>> Rose
>>
>> -----Original Message-----
>> From: Susan Hintz [mailto:srhintz@stanford.edu]
>> Sent: Monday, December 21, 2009 1:05 PM
>> To: qyao@rti.org
>> Cc: adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
>> Subject: the analyses thus far
>>
>> Hi Qing
>>
>> Looking closely at these tables, the numbers just do not seem to add
>> up - or maybe I am just not understanding.
>>
>> We previously determined that among the patients enrolled in SUPPORT
>> Neuroimaging and Neurodevelopmental Outcomes secondary for which
>> there was both EARLY and LATE CUS, Reader 1 had read 579 Early and
>> 578 Late, and Reader 2 had read 577 Early and 578 Late. Yet, for
>> instance, looking at the Table labeled Early CUS Data Analysis
>> Ventilation Strategy - Reader 1 (Attached), there are 476 CPAP under
>> "normal reading" (Yes + No) and 502 Surfactant under "normal reading"
>> (Yes + N). That is nearly 1000 patients.
>>
>> Then, if you look down the table and add up the rest of the numbers,
>> it doesn't make sense either. Look at Mod-severe ventricular enlarge
>> for instance. All the Yes and No's for both CPAP and Surfactant
>> comes to 567. For Bilateral grade 3 or 4 or cPVL, all the Yes and
>> Nos for both CPAP and Surfactant comes to 477. Am I missing
>> something? Remember as we discussed, only if the box is ticked does
>> it mean yes.
>>
>> Even when I look at the % calculations, it doesn't make sense even
>> when looking at the numbers you have there. for instance, look at
>> CPAP Grade 1 or 2. 44 + 260 = 304. Yet, you say that 44 is 17%, but
>> if you look at the numbers 44/304 = 14%. Again, am I missing
>> something?
>>
>> Please let me know as soon as possible,
>>
>> Thanks
>>
>> Susan
>> --
>> Susan R. Hintz, M.D., M.S. Epi
>> Associate Professor of Pediatrics
>> Division of Neonatal and Developmental Medicine
>> Stanford University School of Medicine
>> 750 Welch Road, Suite 315
>> Palo Alto, CA 94304
>> ph: 650-723-5711
>> fax: 650-725-8351

--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine

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Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: FW: Physiologic Def for SUPPORT infants
Date: Tuesday, December 22, 2009 12:12:00 PM
Attachments: Physiologic Def for Support Infants.doc

-----Original Message-----
From: Monica Konstantino [mailto:monica.konstantino@yale.edu]
Sent: Tuesday, December 22, 2009 12:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich
Subject: Re: FW: Physiologic Def for SUPPORT infants

Sorry, I thought that I sent it to you already.
Monica

Higgins, Rosemary (NIH/NICHD) [E] wrote:
>
> Can you send us your responses?
> Thanks
> Rose
>
>
>
> ---
>
> *From:* Higgins, Rosemary (NIH/NICHD) [E]
> *Sent:* Friday, December 11, 2009 11:55 AM
> *To:* Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu);
> (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany
> Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy
> Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane
> Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson
> (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica
> Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
> *Cc:* Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin';
> 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu);
> (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org;
> Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu);
> 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu;
> 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard
> (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy,
> Kathleen A; 'Kristi Watterberg'; Kurt Schibler
> [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh
> William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger
> Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David
> (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
> *Subject:* RE: Physiologic Def for SUPPORT infants
>
>
>
> One more item needed:
>

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> For BPD by oxygen definition, did you use:
> _____ Study oximeter
>
> _____ Clinical oximeter
>
>
>
>
>
> ----------
>
> *From:* Higgins, Rosemary (NIH/NICHD) [E]
> *Sent:* Friday, December 11, 2009 11:51 AM
> *To:* (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita
> Hensman; Becky bara; Bethany Ball; Brenda MacKinnon
> (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby
> (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson;
> Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson
> (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica
> Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
> *Cc:* Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin';
> Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu);
> (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org;
> Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda
> Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis
> Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz
> (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi
> Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh;
> MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth
> (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson
> David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs,
> Krisa
> *Subject:* Physiologic Def for SUPPORT infants
> *Importance:* High
>
>
>
> For SUPPORT, the manual states:
> The study pulse oximeters will be applied to the infant within two
> hours following NICU admission. The
>
> assigned PO will remain on the infant and will be removed once the
> infant has been in room air and off
>
> ventilatory support or CPAP for 72 hours, and if oxygen is
> subsequently required a similar altered pulse
>
> oximeter providing the same SpO2 range will be used until 36 weeks PCA.
>
>
>
> For determination of eligibility for the challenge, did you determine
> eligibility using:
> _____ Study oximeter
>
> _____ Clinical oximeter
>

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>
>
> If a challenge occurred, did your site use
>
> _____Study Oximeter
>
> _____Clinical oximeter
>
>
>
>
>
> Let me know by Dec. 17
>
>
>
> Thanks
>
> Rose
>
>
>
> Rosemary D. Higgins, MD
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal Medicine
>
> Eunice Kennedy Shriver National Institute of Child Health and Human
> Development
>
> National Institutesof Health
>
> 6100 Executive Blvd., Room 4B03
>
> MSC 7510
>
> Bethesda, MD 20892
>
> For overnight delivery use Rockville, MD 20852
>
> 301-496-5575
>
> 301-496-3790 (FAX)
>
> higginsr@mail.nih.gov
>
>
>

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For SUPPORT, the manual states:

The study pulse oximeters will be applied to the infant within two hours following NICU admission. The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:

_____ Study oximeter

___X__ Clinical oximeter

If a challenge occurred, did your site use

_____Study Oximeter

___X__Clinical oximeter

For BPD by oxygen definition, did you use:

_____ Study oximeter

___X__ Clinical oximeter

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Zaterka-Baxter, Kristin"
Cc: "Das, Abhik"
Subject: RE: Estimated timing of publication of results from the SUPPORT trial
Date: Tuesday, December 22, 2009 9:28:00 AM

Chalmers is on the DSMC, right?

We can tell him CONFIDENTIALLY that the two abstracts have been submitted to PAS and that the manuscripts are under peer review currently. They have the critical info regarding outcome.

Thanks
Rose
-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, December 22, 2009 9:23 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: FW: Estimated timing of publication of results from the SUPPORT trial

Hi,

What would you like to tell Drs. Chalmers and Fraser; that data for Support will be presented at PAS?

Thanks,
Kris

-----Original Message-----
From: Iain Chalmers [mailto:IChalmers@jameslindlibrary.org]
Sent: Tuesday, December 22, 2009 6:51 AM
To: Zaterka-Baxter, Kristin
Cc: Fraser William Donald
Subject: Estimated timing of publication of results from the SUPPORT trial

Dear Dr Zaterka-Baxter

I have been in touch with Professor William Fraser, chair of the Data monitoring Committee for the COT trial. We would both find it helpful to have an indication of the envisaged timing of the publication of the short term results of the SUPPORT trial, which you kindly sent to us in confidence. Can you help us, please?

Yours sincerely

Iain Chalmers
Chair, BOOST-II UK DMC

-----Original Message-----
From: Iain Chalmers
Sent: 24 November 2009 14:59
To: 'kzaterka@rti.org'

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Cc: 'Cooke, Richard'
Subject: RE: Confidential

Dear Dr Zaterka-Baxter

As you will gather (see below), one of my colleagues has noted an incorrectly labelled column in Table III.

Thank you again for sharing these data with us.

Yours, Iain Chalmers

-----Original Message-----
From: Cooke, Richard [mailto:R.W.I.Cooke@liverpool.ac.uk]
Sent: 23 November 2009 17:06
To: Iain Chalmers
Subject: RE: Confidential

Nice to have got the cooperation, but how are we going to handle this information? I presume that Table 3 has a misprint and the right column is high oxygen. RC

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 22 November 2009 18:12
To: Zaterka-Baxter, Kristin
Cc: Hazel@mchaffie.f9.co.uk; doug.altman@csm.ox.ac.uk; Cooke, Richard; nancyjowens@yahoo.co.uk
Subject: Confidential

Dear Dr Zaterka-Baxter

Thank you very much for Dr Das' letter, and for the confidential paper reporting selected information from the 4th DSMC report for the SUPPORT Trial. My colleagues and I are very grateful for your generosity in sharing this information.

I am copying these messages and the letter and report to all my fellow members of the DMC for the BOOST-2 UK Trial, so that our deliberations can take account of the confidential information you have kindly provided.

Your sincerely

Iain Chalmers

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From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: 18 November 2009 19:10
To: Iain Chalmers
Cc: Hazel@mchaffie.f9.co.uk
Subject: RE: Website Form Enquiry

Thank you very much Dr. Chalmers (and Dr. McHaffie),

Please find attached a cover letter regarding the SUPPORT Trial and the associated data monitoring report. If you feel these data must be shared outside your DSMC, please contact me as we will need prior authorization from the NICHD.

Please feel free to contact me should you have any questions at all.

Thanks again and my apologies for any inconvenience.
Kris

From: Iain Chalmers [mailto:IChalmers@jameslindlibrary.org]
Sent: Wednesday, November 18, 2009 1:50 PM
To: Zaterka-Baxter, Kristin
Cc: Hazel@mchaffie.f9.co.uk
Subject: RE: Website Form Enquiry

Dear Dr Zaterka-Baxter

My DMC colleague Dr McHaffie has sent me your message to her for a response. I have already sent a response to you confirming that I am the DMC Chair for BOOST-II UK, and I am at a loss to understand why you have not been able to contact me using the only email address that I possess. I wish some of the other people who send me messages h experienced similar difficulties!

So now that you have contacted me and dr McHaffie, perhaps you would be kind enough to please let us both know what you wish to contact us.

Yours sincerely

Iain Chalmers.

SIR IAIN CHALMERS
Editor, James Lind Library
The James Lind Initiative
Summertown Pavilion
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Oxford OX2 7LG, UK
Tel: +44 (0)1865 517636 (direct)
+44 (0)1865 517635
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Email: ichalmers@jameslindlibrary.org
Website: www.jameslindlibrary.org

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From
Date: 16 November 2009 20:07:18 GMT
To: hazel@hazelmchaffie.com<mailto:hazel@hazelmchaffie.com>
Subject: Website Form Enquiry

Name: Kris Zaterka-Baxter
Email: kzaterka@rti.org<mailto:kzaterka@rti.org>
Enquiry: Dear Dr. McHaffie,

I am writing to you on behalf of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), part of the U.S. National Institutes of Health, and the Data Safety and Monitoring Committee (DSMC) for the NICHD Neonatal Research Network (Dr. Christine Gleason is active Chair) in regards to final data from the SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) for which RTI International is the Data Coordinating center. The SUPPORT Trial DSMC had recommended we (RTI)share selected data with the DSMC Chairs of on-going similar trials. I am trying to contact the DSMC Chair of the BOOST II UK Trial; Dr. Chalmers. I have failed on two email attenpts and do not have further contacts for him. I have contacted you becuase you are listed on the DSMC roster for this trial and a websearch brought me to your website. I am hoping you can help me contact Dr. Chalmers so I can confirm he !
still is the DSMC Chair as well as his emial address (ichalmers@cochrane.co.uk<mailto:ichalmers@cochrane.co.uk>). Thank you in advance for any assistance.
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
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www.rti.org<http://www.rti.org>

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Monday, December 21, 2009 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Dale Phelps; Wally Carlo
Cc: Abhik Das; Gantz, Marie
Subject: Re: ROP missing outcomes for SUPPORT

Importance: High

I would hold these until we have word about manuscript decisions. We can add these results at that time More importantly, how do these effect the statistics for the ROP outcomes. Can we have these run and se what the new results are?

Thanks
Neil

On 12/15/09 9:15 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
We have the scores back from the three ophthalmologists who reviewed the ROP exams without a final status. Since there are 3 scores for each individual infant, can we go with "majority rule" to develop a response for NEJM if asked about the 7% missing ROP outcomes? Let me know what you think

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Friday, December 18, 2009 4:42 PM
To: Abhik Das; Gantz, Marie; Wally Carlo; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Analyses

Many thanks Abhik
That is great
Neil

On 12/18/09 10:08 AM, "Abhik Das" <adas@rti.org> wrote:

> Yes Sir, you are the PI!
>
> ...My thought was that I did not want to overburden Marie with the
> impending re-analyses that would very likely result from the NEJM
> reviews. I also could not find any secondary analyses specified in the
> protocol regarding the FiO2 data (perhaps that was a given). In any
> case, Marie will work on these analyses, but would likely not be able
> to finish them before the holidays.
>
> Thanks
>
> Abhik
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Friday, December 18, 2009 12:17 PM
> To: Gantz, Marie; Wally Carlo; Rich, Wade; Das, Abhik; Higgins,
> Rosemary
> (NIH/NICHD) [E]
> Subject: Re: SUPPORT Analyses
>
> Hello Everyone
> I understand that you want to wait and see what the journal weants.
> However, I want these analyses as they are essential in understanding
> what we found. I have not seen any FiO2 data as yet and this was the
> purpose of the oximeters. That is the reason for the oximeter
> separation and we have not even proven as we did for the initial DSMC
> stoppage that there was a separation.
> Please let me know if you do not want these and why.
> Otherwise, can we get started looking at these?
> Thanks
> Neil
> Principal Investigator (I think!!)
>
> Hi Everyone
> I would like to ask that we run the following in anticipation of any

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> reviewers questions I would like to see an FiO2 analysis - ie the
> actual difference in FiO2 by day for the first 14 days between the 2
> SpO2 groups, and after 14 days The oximeters were designed to separate
> the actual FiO2 exposure of these 2 groups.
> In addition I would like an analysis of the SpO2 durations of < 80% >
> 96% and durations of SpO2 < 75%, < 70% < 60% and < 50% for the 2 groups.
> I suspect this may be helpful in looking at the exposure to severe
> hypoxia.
> Marie can you begin these??
> All the best for Christmas and the New Year to everyone and thanks
> again for a great job!!!!!
> Thanks
> Neil

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Fw: SUPPORT Analyses
Date: Friday, December 18, 2009 12:25:13 PM

If there were predefined secondary analyses in the protocol, this may be ok. If not (or vague) we should probably have a clear analysis plan prior to moving thid along. What do you think??
Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Gantz, Marie <mgantz@rti.org>; Wally Carlo <wcarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>; Abhik Das <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Dec 18 12:16:54 2009
Subject: Re: SUPPORT Analyses

Hello Everyone
I understand that you want to wait and see what the journal weants. However, I want these analyses as they are essential in understanding what we found. I have not seen any FiO2 data as yet and this was the purpose of the oximeters. That is the reason for the oximeter separation and we have not even proven as we did for the initial DSMC stoppage that there was a separation.
Please let me know if you do not want these and why.
Otherwise, can we get started looking at these?
Thanks
Neil
Principal Investigator (I think!!)

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I would like to see an FiO2 analysis – ie the actual difference in FiO2 by day for the first 14 days between the 2 SpO2 groups, and after 14 days
The oximeters were designed to separate the actual FiO2 exposure of these 2 groups.
In addition I would like an analysis of the SpO2 durations of < 80% > 96% and durations of SpO2 < 75%, < 70% < 60% and < 50% for the 2 groups. I suspect this may be helpful in looking at the exposure to severe hypoxia.
Marie can you begin these??
All the best for Christmas and the New Year to everyone and thanks again for a great job!!!!!
Thanks
Neil

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From: Karen Osborne RN
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: RE: Physiologic Def for SUPPORT infants
Date: Thursday, December 17, 2009 3:56:34 PM

Please see responses below.

Thanks and very Happy Holidays to you!

Karen

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 9:51 AM
To: (gloria.siaw@duke.edu); Karen Osborne RN; Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Bradley Yoder; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

For SUPPORT, the manual states:
The study pulse oximeters will be applied to the infant within two hours following NICU admission. The
assigned PO will remain on the infant and will be removed once the infant has been in room air and off
ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
___ X __ Study oximeter
___ X _ Clinical oximeter 5 patients

If a challenge occurred, did your site use
__ X ___Study Oximeter
__ X __Clinical oximeter 1 patient

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For BPD by oxygen definition, did you use:

X Study oximeter

X Clinical oximeter 1 patient

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Sood, Beena
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Shankaran, Seetha; Bara, Rebecca
Subject: RE: Physiologic Def for SUPPORT infants
Date: Wednesday, December 16, 2009 10:45:40 AM

Dr Higgins,
At WSU, we used clinical oximeters – Becky has described the procedure we followed below:

"If our SUPPORT infants were on study oximeters at 36 weeks 0 days (still on oxygen), the study oximeters were removed at just about midday and replaced with clinical oximeters. Challenge criteria were then based on oxygen sats documented the rest of that day and the midnight hours of 36 weeks 1 day. Documentation of oxygen saturations using an unaltered oximeter is the only way to determine a baby's true eligibility. So...

In determining the physiologic definition of BPD eligibility (challenge criteria) we used clinical oximeters. If a challenge occurred, it was done using a clinical oximeter."

Let me know if there are any other questions

Thanks
Beena

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; Shankaran, Seetha; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:
_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM

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To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"; "Rich, Wade"; "Wally Carlo"; "Gantz, Marie"; "Abhik Das"
Subject: RE: ROP missing outcomes for SUPPORT
Date: Tuesday, December 15, 2009 3:21:00 PM

I would like Dale's opinion as she has done this in trials previously, but had intended to await the review from NEJM prior to performing any analyses

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 15, 2009 3:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Finer, Neil; Wally Carlo; Gantz, Marie; Abhik Das
Subject: Re: ROP missing outcomes for SUPPORT
Importance: High

Hi Rose and Wally
I would like to see the analyses redone for ROP outcomes using these adjudications. Can Marie rune these using thjeir decisions??
Thanks
Neil

On 12/15/09 9:15 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
We have the scores back from the three ophthalmologists who reviewed the ROP exams without a final status. Since there are 3 scores for each individual infant, can we go with "majority rule" to develop a response for NEJM if asked about the 7% missing ROP outcomes? Let me know what you think

Thanks
Rose

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, December 15, 2009 3:10 PM
To: Gantz, Marie; Wally Carlo; Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Analyses

Hi Everyone
I would like to ask that we run the following in anticipation of any reviewers questions I would like to see an FiO2 analysis – ie the actual difference in FiO2 by day for the first 14 days between the 2 SpO2 groups, and after 14 days The oximeters were designed to separate the actual FiO2 exposure of these 2 groups.
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Marie can you begin these??
All the best for Christmas and the New Year to everyone and thanks again for a great job!!!!!
Thanks
Neil

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Sent: Tuesday, December 15, 2009 3:05 PM
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Subject: Re: ROP missing outcomes for SUPPORT

Importance: High

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Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 6:51:42 PM

From: Bethany Ball <mbball@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Krisa Van Meurs <vanmeurs@stanford.edu>
Sent: Mon Dec 14 18:17:36 2009
Subject: Re: Physiologic Def for SUPPORT infants

Hi Rose,

I've gone back and double checked all of our patients and confirmed the following:

> For determination of eligibility for the challenge, did you determine eligibility using:
> _____ Study oximeter
> __X___ Clinical oximeter
>
> If a challenge occurred, did your site use
> _____Study Oximeter
> __X___Clinical oximeter
>
> For BPD by oxygen definition, did you use:
> _____ Study oximeter
> __X___ Clinical oximeter

Best,
Beth
M. Bethany Ball
Division of Neonatal and Developmental Medicine
Stanford University
650.725.8342

On Dec 11, 2009, at 8:55 AM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> One more item needed:
> For BPD by oxygen definition, did you use:

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_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail);cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
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_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine

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From: Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Krisa Van Meurs
Subject: Re: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 6:17:50 PM

Hi Rose,

I've gone back and double checked all of our patients and confirmed the following:

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
__X___ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
__X___Clinical oximeter

For BPD by oxygen definition, did you use:
_____ Study oximeter
__X___ Clinical oximeter

Best,
Beth
M. Bethany Ball
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Stanford University
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On Dec 11, 2009, at 8:55 AM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

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For BPD by oxygen definition, did you use:
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM

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To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail);cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

For SUPPORT, the manual states:
The study pulse oximeters will be applied to the infant within two hours following NICU admission. The
assigned PO will remain on the infant and will be removed once the infant has been in room air and off
ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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301-496-5575

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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg; Michael Cotten
Subject: Re: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 12:11:57 PM

Dr. Higgins
The study oximeter was used to determine eligibility for the challenge (for those that were still on the study oximeter at 36 weeks) and was also used for the challenge.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

12/11/2009 11:51 AM

To " (gloria.siaw@duke.edu)" <gloria.siaw@duke.edu>, " (Karen.Osborne@hsc.utah.edu)" <Karen.Osborne@hsc.utah.edu>, Angelita Hensman <ahensman@wihri.org>, Becky bara <ae5357@wayne.edu>, Bethany Ball <mbball@leland.stanford.edu>, "Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org)" <bmackinnon@tuftsmedicalcenter.org>, "Cathy Grisby (cathy.grisby@uc.edu)" <cathy.grisby@uc.edu>, Conra Backstrom <CBackstrom@salud.unm.edu>, Diana Vasil <Diana.Vasil@utsouthwestern.edu>, Diane Wilson <dhwilson@iupui.edu>, Elizabeth Billian <du2744@wayne.edu>, Ellen Hale <ellen_hale@oz.ped.emory.edu>, Georgia McDavid <Georgia.E.McDavid@uth.tmc.edu>, "Karen Johnson (karen-johnson@uiowa.edu)" <karen-johnson@uiowa.edu>, Kimberley Fisher <Kimberley.fisher@duke.edu>, Leslie Wilson <ldw@iupui.edu>, Monica Collins <mcollins@peds.uab.edu>, "monica.konstantino@yale.edu" <monica.konstantino@yale.edu>, Nancy Miller <Nancy.Miller@utsouthwestern.edu>, Nancy Newman <nxs5@cwru.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'" <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>, "Finer, Neil" <nfiner@ucsd.edu>, " (Luc.Brion@UTSouthwestern.edu)" <Luc.Brion@utsouthwestern.edu>, " (rohls@unm.edu)" <rohls@unm.edu>, "aaf2@po.cwru.edu" <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>, "alaptook@WIHRI.org" <alaptook@wihri.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, Dennis Wallace <dwallace@rti.org>, Ed Bell <Edward-bell@uiowa.edu>, Ed Donovan <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi Watterberg <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, Michelle Walsh <mcw3@po.cwru.edu>, MIckey Caplan <mcaplan@northshore.org>, "Oh William (E-mail)" <william_oh@brown.edu>, Pablo Sanchez <Pablo.Sanchez@utsouthwestern.edu>, "Poole Kenneth (E-mail)" <poo@rti.org>, Roger Faix <Roger.Faix@hsc.utah.edu>, Ronald GOldberg <goldb008@mc.duke.edu>, Seetha Shankaran

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<sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
<dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
<barbara_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)"
<Jon.E.Tyson@uth.tmc.edu>, "VanMeurs, Krisa"
<vanmeurs@leland.stanford.edu>

Subject Physiologic Def for SUPPORT infants

For SUPPORT, the manual states:

The study pulse oximeters will be applied to the infant within two hours following NICU admission. The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

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_____ Clinical oximeter

If a challenge occurred, did your site use

_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kimberley A Fisher"; "Ronald N Goldberg"; "Michael Cotten"
Subject: RE: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 12:10:00 PM

Was this for all of the questions below?

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Monday, December 14, 2009 12:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg; Michael Cotten
Subject: RE: Physiologic Def for SUPPORT infants

Dr. Higgins
The study oximeter was used for those subjects that were still on study at 36 weeks.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

12/11/2009 11:55 AM

To "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "(gloria.siaw@duke.edu)" <gloria.siaw@duke.edu>, "(Karen.Osborne@hsc.utah.edu)" <Karen.Osborne@hsc.utah.edu>, Angelita Hensman <ahensman@wihri.org>, Becky bara <ae5357@wayne.edu>, Bethany Ball <mbball@leland.stanford.edu>, "Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org)" <bmackinnon@tuftsmedicalcenter.org>, "Cathy Grisby (cathy.grisby@uc.edu)" <cathy.grisby@uc.edu>, Conra Backstrom <CBackstrom@salud.unm.edu>, "'Diana Vasil'" <Diana.Vasil@utsouthwestern.edu>, "'Diane Wilson'" <dhwilson@iupui.edu>, Elizabeth Billian <du2744@wayne.edu>, Ellen Hale <ellen_hale@oz.ped.emory.edu>, Georgia McDavid <Georgia.E.McDavid@uth.tmc.edu>, "Karen Johnson (karen-johnson@uiowa.edu)" <karen-johnson@uiowa.edu>, "'Kimberley Fisher'" <Kimberley.fisher@duke.edu>, "'Leslie Wilson'" <ldw@iupui.edu>, Monica Collins <mcollins@peds.uab.edu>, "monica.konstantino@yale.edu" <monica.konstantino@yale.edu>, Nancy Miller <Nancy.Miller@utsouthwestern.edu>, Nancy Newman <nxs5@cwru.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'" <kzaterka@rti.org>, "'Cunningham, Meg'" <mcunningham@rti.org>, "'Finer, Neil'" <nfiner@ucsd.edu>, "(Luc.Brion@UTSouthwestern.edu)" <Luc.Brion@utsouthwestern.edu>, " (rohls@unm.edu)" <rohls@unm.edu>, "aaf2@po.cwru.edu" <aaf2@po.cwru.edu>, "'Abhik Das'" <adas@rti.org>, "alaptook@WIHRI.org" <alaptook@wihri.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, "'Brenda Poindexter'" <bpoindex@iupui.edu>, "'Carlo Waldemar (E-mail)'" <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "'Dennis Wallace'" <dwallace@rti.org>, "'Ed Bell'" <Edward-bell@uiowa.edu>, "'Ed Donovan'"

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<edward.donovan@cchmc.org>, "'Ehrenkranz Richard (E-mail)'" <richard.ehrenkranz@yale.edu>, "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "'Kristi Watterberg'" <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, "'Michelle Walsh'" <mcw3@po.cwru.edu>, "'MIckey Caplan'" <mcaplan@northshore.org>, "'Oh William (E-mail)'" <william_oh@brown.edu>, "'Pablo Sanchez'" <Pablo.Sanchez@utsouthwestern.edu>, "'Poole Kenneth (E-mail)'" <poo@rti.org>, "'Roger Faix'" <Roger.Faix@hsc.utah.edu>, "'Ronald GOldberg'" <goldb008@mc.duke.edu>, "'Seetha Shankaran'" <sshankar@med.wayne.edu>, "'Stevenson David (E-mail)'" <dstevenson@stanford.edu>, "'Stoll Barbara (E-mail)'" <barbara_stoll@oz.ped.emory.edu>, "'Tyson Jon (E-mail)'" <Jon.E.Tyson@uth.tmc.edu>, "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>

Subject RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:

_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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_____ Study oximeter
_____ Clinical oximeter

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If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 10:51:00 AM

From: Hensman, Angelita [mailto:AHensman@WIHRI.org]
Sent: Monday, December 14, 2009 10:45 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Laptook, Abbot
Subject: RE: Physiologic Def for SUPPORT infants

Please see answers below.

Thanks

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Hensman, Angelita; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; Laptook, Abbot; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use: Per FiO2 documentation in medical record at 36 weeks.
_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda

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Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
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__X___ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
__X___Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Physiologic Def for SUPPORT infants
Date: Monday, December 14, 2009 8:33:49 AM

From: Mackinnon, Brenda <bmackinnon@tuftsmedicalcenter.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Frantz, Ivan <ifrantz@tuftsmedicalcenter.org>
Sent: Mon Dec 14 06:57:00 2009
Subject: RE: Physiologic Def for SUPPORT infants

Hi Rose,
In general I did everything once the baby was off the study oximeter. I felt the data was more accurate that way. I thought if I used the altered, blinded study oximeter I wouldn't really know if the baby had BPD or not.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
__x___ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
___x__Clinical oximeter

For BPD by oxygen definition, did you use:
_____ Study oximeter
___x__ Clinical oximeter

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper (b) (6)

Phone: 617-636-1218
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Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44

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Boston, Ma 02111

Beeper # (b)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Mackinnon, Brenda; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Frantz, Ivan; Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
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_____ Study oximeter
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If a challenge occurred, did your site use
_____Study Oximeter
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Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch

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Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Conra Lacy"
Cc: "Kristi Watterberg"
Subject: RE: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 4:35:00 PM

Thanks
We have that info

Rose

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]
Sent: Friday, December 11, 2009 4:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kristi Watterberg
Subject: Re: Physiologic Def for SUPPORT infants

Dr. Higgins,
The PHYO2BASE form, Question A.2. asks what type of oximeter is used in the challenge. The answer in that field may be helpful. If it says anything other than "Masimo" it was not a study oximeter. If it says Masimo you would need to know if the center used Masimo monitors clinically. New Mexico does not.
Just a thought,
Connie

Conra (Connie) Backstrom Lacy
University of New Mexico
Manager, Clinical Research
(505) 272-0367
pager (505) 951(b)
fax (505) 272-5589
cbackstrom@salud.unm.edu

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 4:19:00 PM
Attachments: New Mexico SUPPORT Oximeters 36weeks.doc

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]
Sent: Friday, December 11, 2009 4:15 PM
To: Nancy Newman; (gloria.siaw@duke.edu); Kimberley Fisher; (Karen.Osborne@hsc.utah.edu); Diane Wilson; Leslie Wilson; Bethany Ball; Higgins, Rosemary (NIH/NICHD) [E]; Ellen Hale; Monica Collins; Brenda MacKinnon(bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Karen Johnson (karen-johnson@uiowa.edu); Georgia McDavid; Diana Vasil; Nancy Miller; Becky bara; Elizabeth Billian; Angelita Hensman; monica.konstantino@yale.edu
Cc: Oh William (E-mail); Ed Donovan; Kurt Schibler [kurt.schibler@cchmc.org]; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix; Brenda Poindexter; Krisa VanMeurs; Archer, Stephanie (NIH/NICHD) [E]; cotte010@mc.duke.edu; Ronald GOldberg; Seetha Shankaran; MIckey Caplan; Stoll Barbara(E-mail); CarloWaldemar (E-mail); aaf2@po.cwru.edu; Michelle Walsh; Abhik Das; Dennis Wallace; Kristin' 'Zaterka-Baxter; Meg Cunningham; Poole Kenneth (E-mail); Kristi Watterberg; Stevenson David (E-mail); Ivan Frantz(ifrantz@tuftsmedicalcenter.org); Ambal(ambal@uab.edu); Neil Finer; Ed Bell; (rohls@unm.edu); Tyson Jon (E-mail); Kathleen A Kennedy; (Luc.Brion@UTSouthwestern.edu); PabloSanchez; alaptook@WIHRI.org; EhrenkranzRichard (E-mail)
Subject: Re: Physiologic Def for SUPPORT infants

Dr. Higgins,
In New Mexico the Study oximeter was kept on the patient until 36 weeks, death, transfer, or room air. Therefore, the study oximeter was used to determine eligibility for RA challenge, and to record the use of oxygen at 36 weeks. As you can see from the attached table, 16 subjects were alive at 36 weeks. Four of those were on clinical oximeters because they were in another hospital. One more was on a clinical oximeter because they were in room air. Of the 4 on whom the challenge was done, 3 were still on the study oximeter at the time of the challenge. One challenge was done on a clinical oximeter because it was done after the 36 weeks date, but the subject had been on the study oximeter at 36 weeks.
I hope this answers your questions.
Connie

Conra (Connie) Backstrom Lacy
University of New Mexico
Manager, Clinical Research
(505) 272-0367
pager (505) 95[redacted](b)
fax (505) 272-5589
cbackstrom@salud.unm.edu

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/11/2009 9:50 AM >>>
For SUPPORT, the manual states:
The study pulse oximeters will be applied to the infant within two hours following NICU admission. The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter

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_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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New Mexico SUPPORT Oximeters @ 36 weeks

Subject ID	36 week Status	RA Trial	Oximeter	Comments
(b) (6)	CPAP	no	study	
	died		none	
	NCO2	yes	clinical	Off study oximeter before RA trial
	Room air	no	clinical	at another hospital
	NC O2	no	clinical	at another hospital
	NC O2	no	clinical	at another hospital
	died		none	
	ventilator	no	study	
	died		none	
	NC O2	yes	study	
	NC O2	no	study	Not eligible for RA trial
	NC O2	no	clinical	Withdrew, at another hospital
	NC O2	no	study	refused RA trail
	Room Air		clinical	
	NC O2	yes	study	
	died		none	
	NC O2	yes	study	
	CPAP	no	study	
	High flow NC	no	study	
	died		none	
	ventilator	no	study	

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Nancy Miller"
Subject: RE: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 4:04:00 PM

Ok
Thanks
Rose

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Friday, December 11, 2009 4:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Yes, it was 68. Infant was originally at 2 LPM with an FiO2 of .21 and when the flow was turned down to 0.5 LPM that's when the sats plunged.

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/11/2009 2:55 PM >>>
Do you mean 88 or 68?

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Friday, December 11, 2009 3:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Diana Vasil; Pablo Sanchez
Subject: Re: Physiologic Def for SUPPORT infants

Rose,
I looked at the completed PHY02BASE forms for our SUPPORT babies who had challenges. According to my records one of our infants was tested with a Masimo (not sure why or how it happened). All of the other infants had clinical oximeters used for eligibility, the challenge, and for BPD by oxygen definition. The infant, who had the Masimo in place, failed when the sats went to 68 so the outcome would have been the same with a clinical oximeter.
Hope this answers your questions.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/11/2009 10:50 AM >>>
For SUPPORT, the manual states:
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For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

For BPD by oxygen definition, did you use:
_____ Study oximeter
_____ Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Nancy Miller"
Cc: "Diana Vasil"; "Pablo Sanchez"
Subject: RE: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 3:55:00 PM

Do you mean 88 or 68?

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Friday, December 11, 2009 3:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Diana Vasil; Pablo Sanchez
Subject: Re: Physiologic Def for SUPPORT infants

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Hope this answers your questions.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/11/2009 10:50 AM >>>
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Let me know by Dec. 17

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 2:45:00 PM

From: Monica Collins [mailto:MCollins@peds.uab.edu]
Sent: Friday, December 11, 2009 2:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Which question is this? We recorded 36 week oxygen use on the respiratory sheet (NG07) and supp11 with the study pulse oximeter if the baby was still on it.
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; Wally Carlo, M.D.; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:
_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran;

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Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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If a challenge occurred, did your site use
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_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 2:45:00 PM

Wally – see below!

From: Monica Collins [mailto:MCollins@peds.uab.edu]
Sent: Friday, December 11, 2009 2:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Which question is this? We recorded 36 week oxygen use on the respiratory sheet (NG07) and supp11 with the study pulse oximeter if the baby was still on it.
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
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Subject: RE: Physiologic Def for SUPPORT infants

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Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran;

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Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 2:44:00 PM

From: Monica Collins [mailto:MCollins@peds.uab.edu]
Sent: Friday, December 11, 2009 2:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

At UAB, determination of eligibility by study pulse oximeter used on 36 week PCA day. If infant had challenge done, it was done with a clinical pulse oximeter.
Study PO left on baby on day 36 week because 4 data points were required on that day. After the study PO was removed, the infant, if requiring challenge, had a 5 minute period of baseline on a clinical PO, and then the challenge was done.
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
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assigned PO will remain on the infant and will be removed once the infant has been in room air and off
ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

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Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Friday, December 11, 2009 1:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for GDB access

Rose
I am happy to participate by phone
What is the main question being asked
Neil

Sent from my iPhone

On Dec 11, 2009, at 5:51 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov > wrote:

> Neil
> Luc is interested in merging SUPPORT and GDB data and will present a
> concept at the upcoming SC meeting.
>
> We went to a procedure of "concepts" about 2 years ago to garner SC
> interest in a topic prior to development of a full protocol. Let me
> know if you want to join (either in person or on the phone). The
> meeting is Feb 11-12.
>
>
> Thanks
> Rose
>
> -----Original Message-----
> From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
> Sent: Friday, December 11, 2009 12:28 AM
> To: Higgins, Rosemary (NIH/NICHD) [E];
> 'Barbara.Stoll@oz.ped.emory.edu'
> Cc: JACLYN LEVAN; Pablo Sanchez
> Subject: RE: Request for GDB access
>
> Rose:
>
> Thanks again.
> The tentative title is "Impact of initiating the SUPPORT trial on
> management and outcome of age-matched non-participants."
>
> Best regards,
>
> Luc
>
> Luc P. Brion, MD
> Professor of Pediatrics
> Director, Fellowship Training Program in Neonatal-Perinatal Medicine

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> The University of Texas Southwestern Medical Center at Dallas
> 5323 Harry Hines Boulevard, STOP 9063
> Dallas, TX 75390-9063
> Office: (214) 648-2835
> Fax: (214) 648-2481
> Pager: (972) 326-(b)
> luc.brion@utsouthwestern.edu
>
>
>>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>>>> 12/4/2009 7:42 AM >>>
> Here is the outline - if you get the concept by jan 6, this will be
> fine - please send me the title
>
> Thanks
> Rose
>
> -----Original Message-----
> From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
> Sent: Thursday, December 03, 2009 10:11 AM
> To: Higgins, Rosemary (NIH/NICHD) [E];
> 'Barbara.Stoll@oz.ped.emory.edu'
> Cc: Pablo Sanchez
> Subject: Re: Request for GDB access
>
> Is the deadline 1/4/10?
> Luc
>
> Luc P. Brion, MD
> Professor of Pediatrics
> Director, Fellowship Training Program in Neonatal-Perinatal Medicine
> The University of Texas Southwestern Medical Center at Dallas
> 5323 Harry Hines Boulevard, STOP 9063
> Dallas, TX 75390-9063
> Office: (214) 648-2835
> Fax: (214) 648-2481
> Pager: (972) 326-(b)
> luc.brion@utsouthwestern.edu
>
>
>>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>>>> 12/3/2009 7:43 AM >>>
> I can send the protocol outline tomorrow
>
> ----- Original Message -----
> From: Luc Brion <Luc.Brion@UTSouthwestern.edu>
> To: Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu
> >
> Sent: Thu Dec 03 08:40:06 2009
> Subject: Re: Request for GDB access
>

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> Hi Barbara:
> Thanks a lot for your response
> Luc
>
> Luc P. Brion, MD
> Professor of Pediatrics
> Director, Fellowship Training Program in Neonatal-Perinatal Medicine
> The University of Texas Southwestern Medical Center at Dallas
> 5323 Harry Hines Boulevard, STOP 9063
> Dallas, TX 75390-9063
> Office: (214) 648-2835
> Fax: (214) 648-2481
> Pager: (972) 326(b)
> luc.brion@utsouthwestern.edu
>
>
>>>> "Barbara Stoll" <Barbara.Stoll@oz.ped.emory.edu> 12/2/2009 10:21
>>>> PM >>>
>
> Hi Luc
> Pablo can give you the format for a concept proposal to expand your
> Parkland study to the entire Network cohort
> The strudy will be reviewed by the Subcommittee.
> Given the rush to get PAS presentation completed, I assume this may
> need
> to wait until those presentations are completed-- although there may
> be a
> window now between submission of abstracts and notice of which are
> accepted and will be presented
>
>
>
> Regards
>
> BJS
>
>
>
>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 1:51:00 PM

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Friday, December 11, 2009 1:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wilson, Leslie Dawn
Subject: RE: Physiologic Def for SUPPORT infants

Rose,
We followed the manual guidelines for use of the study oximeters – so any baby on oxygen indeed was still on a study oximeter up until 36 weeks. We determined if babies were eligible for a challenge at 36 weeks – then notified the study RT that a challenge needed to be performed sometime in the next week. So, in general, all challenges would be performed on a clinical oximeters because the study oximeters was removed at 36 weeks and the challenge occurred in that next week after 36 weeks. What we don't know for sure is how efficient the RTs were in doing the challenge – in general, I think it is fair to say that babies would have all been on clinical oximeters – but could there have been a few babies here or there that the challenge was done on the same exact day that the baby hit 36 weeks and maybe the study oximeters was still on – possibly – but I really don't think we were that speedy in getting the challenges done exactly on the day the baby hit 36 weeks but we were efficient at removing the study oximeters on exactly that day. Clear as mud? I don't think any of the SUPPORT forms ask for the exact day the challenge was done, did they? Let us know if this doesn't make sense. Brenda and Leslie

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; Herron, Dianne E; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; Wilson, Leslie Dawn; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Poindexter, Brenda B; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:
_____ Study oximeter
_____ Clinical oximeter

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

For SUPPORT, the manual states:
The study pulse oximeters will be applied to the infant within two hours following NICU admission. The
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oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 1:47:00 PM

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Friday, December 11, 2009 1:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tyson, Jon E; Kennedy, Kathleen A
Subject: RE: Physiologic Def for SUPPORT infants

UT – Houston site 18
For determination of eligibility for the challenge, did you determine eligibility using:
__X___ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_X__Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Mcdavid, Georgia E; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

For SUPPORT, the manual states:
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ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter

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_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:55:00 PM

From: Grisby, Cathy (grisbyca) [mailto:grisbyca@ucmail.uc.edu]
Sent: Friday, December 11, 2009 12:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
___X__ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
__X___Clinical oximeter

One more item needed:
For BPD by oxygen definition, did you use:
_____ Study oximeter
__X___ Clinical oximeter

That's from Cincinnati.
Have a nice weekend!
Cathy

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:50 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Grisby, Cathy (grisbyca); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; CHM-Donovan, Edward (edward.donovan); Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; CHM-Schibler, Kurt (kurt.schibler); Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants

For SUPPORT, the manual states:
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altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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higginsr@mail.nih.gov

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From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:24:35 PM
Importance: High

>For SUPPORT, the manual states:
>The study pulse oximeters will be applied to the infant within two
>hours following NICU admission. The
>assigned PO will remain on the infant and will be removed once the
>infant has been in room air and off
>ventilatory support or CPAP for 72 hours, and if oxygen is
>subsequently required a similar altered pulse
>oximeter providing the same SpO2 range will be used until 36 weeks PCA.
>
>For determination of eligibility for the challenge, did you
>determine eligibility using:
>_____ Study oximeter
>___X__ Clinical oximeter
>
>If a challenge occurred, did your site use
>_____Study Oximeter
>___X__Clinical oximeter
>
>
>Let me know by Dec. 17
>
>Thanks
>Rose
>
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:29:00 PM

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Friday, December 11, 2009 12:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu
Subject: RE: Physiologic Def for SUPPORT infants

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:
_____ Study oximeter
__xx___ Clinical oximeter

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Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran;

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Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:24:00 PM

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Friday, December 11, 2009 12:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Rose,
Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and others on the clinical one. If you need me to send specifics, I can.

Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (319) 356-(b) ask for pager (b)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Elizabeth Billian; Ellen Hale; Georgia McDavid; Johnson, Karen; 'Kimberley Fisher'; 'Leslie Wilson'; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; Bell, Edward; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa
Subject: RE: Physiologic Def for SUPPORT infants

One more item needed:
For BPD by oxygen definition, did you use:

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_____ Study oximeter
_____ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

For SUPPORT, the manual states:
The study pulse oximeters will be applied to the infant within two hours following NICU admission. The
assigned PO will remain on the infant and will be removed once the infant has been in room air and off
ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:15:00 PM

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Friday, December 11, 2009 12:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Emory 09

For SUPPORT, the manual states:
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_____ Clinical oximeter

If a challenge occurred, did your site use

_____Study Oximeter

__X___Clinical oximeter

Let me know by Dec. 17

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Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:15:00 PM

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Friday, December 11, 2009 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu
Subject: RE: Physiologic Def for SUPPORT infants

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Subject: Physiologic Def for SUPPORT infants
Importance: High

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ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse
oximeter providing the same SpO2 range will be used until 36 weeks PCA.

For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
___xx__ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_xx____Clinical oximeter

Let me know by Dec. 17

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Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:14:00 PM

Please tally

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Friday, December 11, 2009 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Physiologic Def for SUPPORT infants

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

One more item needed:

For BPD by oxygen definition, did you use:
_____ Study oximeter (for possibly first 3-4 subjects)

__X___ Clinical oximeter

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 11, 2009 11:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

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Subject: Physiologic Def for SUPPORT infants
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oximeter providing the same SpO2 range will be used until 36 weeks PCA.

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_____ Clinical oximeter

If a challenge occurred, did your site use

_____Study Oximeter

_____Clinical oximeter

Let me know by Dec. 17

Thanks

Rose

Rosemary D. Higgins, MD

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Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Tyson, Jon E"
Cc: "Wally Carlo, M.D."; "nfiner@ucsd.edu"
Subject: RE: Physiologic Def for SUPPORT infants
Date: Friday, December 11, 2009 12:14:00 PM

See fu email

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Friday, December 11, 2009 11:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.; nfiner@ucsd.edu
Subject: RE: Physiologic Def for SUPPORT infants

Rose, if you are trying to address the principal issue I raised, this question doesn't address it- my question is about whether the study oximeter was used in determining BPD by oxygen administration at 36 weeks.

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 11, 2009 10:51 AM
To: (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Mcdavid, Georgia E; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa
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For determination of eligibility for the challenge, did you determine eligibility using:
_____ Study oximeter
_____ Clinical oximeter

If a challenge occurred, did your site use
_____Study Oximeter
_____Clinical oximeter

Let me know by Dec. 17

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Furey, Anne M"
Cc: "jdavis@tuftsmedicalcenter.org"; "Frantz, Ivan"
Subject: RE: Breathing Outcome Questions
Date: Wednesday, December 09, 2009 1:27:00 PM

This will be fine – can you send me a list of the sites so that I can let the Steering Committee know who is using the forms? The request came in for using them in a multi-center study headed by TUFTS.

Thanks
Rose

From: Furey, Anne M [mailto:afurey@tuftsmedicalcenter.org]
Sent: Wednesday, December 09, 2009 12:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcome Questions

Rose,

My understanding is that our group previously asked you if we could use the SUPPORT breathing outcome questions for another NIH-funded study that our Chief of Newborn Medicine, Dr. Jonathan Davis, is heading and that this permission had been granted.

The study sites need to submit these questions to the IRB. We want to make sure that you are aware that this study will start very soon with the plan to use the SUPPORT questions and that you don't have any new found concerns.

The purpose of Dr. Davis' study is to find better ways to predict long-term breathing outcomes in infants who were born very premature and to then use these predictors in future research studies that look at treatments to prevent respiratory problems.

Please confirm we can move forward using the breathing outcome questions.

Thanks,
Anne

Anne Furey, MPH
Floating Hospital for Children at Tufts Medical Center
800 Washington Street, Box 44
Boston, MA 02111
Phone: 617-636-7134
Fax: 617-636-1456
afurey@tuftsmedicalcenter.org

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From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: antenatal consent paper
Date: Tuesday, December 08, 2009 10:52:37 AM

Rose,

Interesting idea for a paper. Appreciate the chance to read it.

Couple things you might want to check

on the last table: (b) (5) [redacted]

The table on (b) (5) [redacted].

Second to last paragraph before conclusion: repeated sentence, starting "In our study"

Carol

Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "edward-bell@uiowa.edu"
Subject: Fw: New England Journal of Medicine - 09-11783
Date: Wednesday, December 02, 2009 1:25:06 PM

----- Original Message -----
From: onbehalfof+editorial+nejm.org@manuscriptcentral.com <onbehalfof+editorial+nejm.org@manuscriptcentral.com>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@wihri.org <alaptook@wihri.org>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; roger.faix@has.utah.edu <roger.faix@has.utah.edu>; adas@rti.org <adas@rti.org>; poo@rti.org <poo@rti.org>; nambalavanan@peds.uab.edu <nambalavanan@peds.uab.edu>; (b) (6) (b) (6) edward.donovan@cchmc.org <edward.donovan@cchmc.org>; vivek.narendran@cchmc.org <vivek.narendran@cchmc.org>; nxs5@cwru.edu <nxs5@cwru.edu>; ifrantz@tufts-nemc.org <ifrantz@tufts-nemc.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; susie.buchter@oz.ped.emory.edu <susie.buchter@oz.ped.emory.edu>; (b) (6) (b) (6) >; nirupama_laroia@urmc.rochester.edu <nirupama_laroia@urmc.rochester.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; vanmeurs@leland.stanford.edu <vanmeurs@leland.stanford.edu>; bsood@med.wayne.edu <bsood@med.wayne.edu>; sduara@miami.edu <sduara@miami.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; edward.bell@uiowa.edu <edward.bell@uiowa.edu>; vineet.bhandari@yale.edu <vineet.bhandari@yale.edu>; kwatterberg@salud.unm.edu <kwatterberg@salud.unm.edu>; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6) >
Sent: Tue Dec 01 16:42:02 2009
Subject: New England Journal of Medicine - 09-11783

Dear Dr. Finer and co-authors,

Thank you for submitting your manuscript, "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your manuscript ID is 09-11783.

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Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School

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10 Shattuck Street
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From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: Confidential SUPPORT papers for submission to NEJM
Date: Wednesday, December 02, 2009 12:02:07 PM

Rose,
Nicely done. Please let us know if this is accepted by NEJM—it would be nice to do a joint press release. I like (b) (5) [redacted].

I have some comments that you and your co-authors can take or leave:

Carlo paper:
In Methods—(b) (5) [redacted]

Page 20, "(b) (5) [redacted] The ref implies it was completed

Table 1—are there any (b) (5) [redacted]
Comment in the results/discussion about duration of (b) (5) [redacted]

For the Finer paper:
Many of the abbreviations aren't defined—would do that for each (define then use abbrev)—ie. CPAP, DR, BPD, PEEP, NRP, MAP, PDA, etc.
Would the title be more accurate to say (b) (5) [redacted]

Methods: would be helpful to clarify what (b) (5) [redacted]

First para of Intro, sentence starting "Surfactant" –need to add the word "has" before "not been

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found"

How much (b) (5) [redacted]

How was the (b) (5) [redacted] —perhaps add to methods?
How was (b) (5) [redacted]

In results: 3rd para, (b) (5) [redacted]

Table A2–(b) (5) [redacted]

cb

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Lung Developmental Biology and
Pediatric Pulmonary Diseases
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(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 01, 2009 9:58 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Confidential SUPPORT papers for submission to NEJM

Here are close to final drafts of the Two SUPPORT papers-
Thanks for all your help, perseverance and financial support for this study!!
Rose

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, December 01, 2009 9:29 PM
To: Tyson, Jon E
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: Re: Early CPAP paper

Thanks Jon
I appreciate your diligence
The results are clearly presented and qualified - the hand has been dealt to the NEJM Their play, their deck, ?? Texus Holdem???
Be well
Neil

Sent from my iPhone

On Dec 1, 2009, at 2:46 PM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>> wrote:

Thanks, Neil. Wally and you have done a great job with a very difficult study to address fundamental questions in neonatology. I have a few more comments to offer to further enhance the paper:

1) Abstract. Ann apparent oversight: The 2nd sentence of the Results still notes two primary outcomes (BPD by the physiologic definition and BPD by supplemental oxygen) whereas the last sentence of the introduction in the manuscript notes BPD by physiologic definition as the primary outcome and BPD by oxygen administration is later specifically noted as a secondary outcome.
2) While the method to generate the sample size is noted, the power for the primary outcome of the manuscript is not specifically noted.
We should include this (with the increase in enrollment, I would expect it would be >0.80).
3) I like what was done in Wally's paper to indicate the number of significant p values expected by chance with the multiple comparisons of secondary outcomes and subgroup analyses, and this would help to address the published NEJM requirements for subgroup analyses. In my view, you will be criticized for not emphasizing hat the subgroup difference in deaths was not pre-hypothesized. (The reason for their requirements is that except in narrowly defined circumstances, he best estimate of treatment effect in subgroups has usually been the overall treatment effect.)
4) To repeat a recommendation for Wally's paper: Provide the p value for the interaction when you present the subgroup analyses and add to the appendix a table that provides the rate of the primary outcome in each of the four treatment cells. This can be very easily done. As noted in standards for factorial designs, "accurate interpretation of factorial trials depends on the transparent reporting of data for each treatment cell' (McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials. A systematic review JAMA 2003; 289:2545-2553.) A point often not understand by clinicians is that there can be clinically important effects of using two interventions together even in the absence of a statistical interaction. Such effects can be suggested by providing the outcomes for each cell of these tables. (See comment about using interaction ratios and calculations in Table 6 in the reference above which I would be happy to discuss if you want). After reading this you may agree that it also add such tables to the appendix for death and for BPD by the physiologic definition.
5) Ref the secondary outcome of death or BPD by supplemental oxygen: see my last (long) comment in my e mail to Wally. If the problem I noted occurred in multiple centers, this would bias the results of Wally's analyses of BPD to favor the low oxygen sat group. Though the way in which BPD was identified needs to be spelled out, this problem would not

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bias the results of your analyses of BPD as both treatment arms had a nearly identical proportion of infants in the two oxygen saturation ranges.
6) The manuscript still contains abbreviations that NEJM has not allowed before, and the Journal explicitly discourages abbreviations in the instructions to authors.

Again, congratulations, Neil. Here's hoping both manuscripts will be accepted, and the Journal won't make your life miserable in getting to that point.

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Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston
6431 Fannin St., MSB 2.106
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voice 713-500-5651
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 30, 2009 3:42 PM
To: Rich, Wade; Gantz, Marie; 'Poole Kenneth (E-mail)'; 'Nancy Newman'; Ambal (ambal@uab.edu<mailto:ambal@uab.edu>); Anthony Piazza; 'Susie Buchter'; 'Vivek.Narendran@cchmc.org<mailto:'Vivek.Narendran@cchmc.org>'; 'vineet.bhandari@yale.edu<mailto:'vineet.bhandari@yale.edu>'; 'Brenda Morris'; 'Laroia, Nirupama'; Phelps, Dale; sduara@miami.edu<mailto:sduara@miami.edu>; 'Sood, Beena'; 'Michael O`Shea'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>); (rohls@unm.edu<mailto:rohls@unm.edu>); aaf2@po.cwru.edu<mailto:aaf2@po.cwru.edu>; Abhik Das; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Brad Yoder (Bradley.yoder@hsc.utah.edu<mailto:Bradley.yoder@hsc.utah.edu>); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa
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Subject: Confidential SUPPORT papers for submission to NEJM

Hi
Attached are the two SUPPORT papers for submission to NEJM. They will be submitted later this week.

Thanks to everyone for the quick work in writing the papers and the patience and endurance to conduct this important trial!!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutesof Health
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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, December 01, 2009 7:16 PM
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Oxygen Saturation Goals

Hi Wally
That has been his style and I mentioned that on our conference call I have ignored his comments from then onward
Sweet work on the manuscript and thanks for taking it on Be well Neil

Sent from my iPhone

On Dec 1, 2009, at 2:08 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>> wrote:

I was thinking about whether to respond to Jon's comments. I find that his comments have come way too late and that many of them have been addressed already but he is not aware of it. I am not sure why he prefers to be copying everyone at this point.

Wally

Wally Carlo, M.D.
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Cell: 205 266 (b) [redacted]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, December 01, 2009 4:03 PM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu<mailto:'nfiner@ucsd.edu>'
Subject: Re: Oxygen Saturation Goals

The papers have been submitted, so we will see what the editors say. The papers are uploaded so there is nothing more to do at this point (unless folks want to propose secondary analyses in the form of a written proposal).

Thanks to both of you, especially Neil for asking about submission earlier today!!!!
Congratulations, hopefully

Rose
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>

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To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <nfiner@UCSD.Edu<mailto:nfiner@UCSD.Edu>>
Sent: Tue Dec 01 16:58:18 2009
Subject: FW: Oxygen Saturation Goals
Hi Rose:

All his identified typos had been corrected already. We could take the asterisks of two rows in Table 2 as he suggests.

How do you want me to handle his other suggestions?

Wally

Wally Carlo, M.D.
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Cell: 205 266 (b)

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, December 01, 2009 3:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; 'Poole Kenneth (E-mail)'; 'Nancy Newman'; Ambal (ambal@uab.edu<mailto:ambal@uab.edu>); Anthony Piazza; 'Susie Buchter'; 'Vivek.Narendran@cchmc.org<mailto:'Vivek.Narendran@cchmc.org>'; 'vineet.bhandari@yale.edu<mailto:'vineet.bhandari@yale.edu>'; 'Brenda Morris'; 'Laroia, Nirupama'; Phelps, Dale; sduara@miami.edu<mailto:sduara@miami.edu>; 'Sood, Beena'; 'Michael O`Shea'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>); (rohls@unm.edu<mailto:rohls@unm.edu>); aaf2@po.cwru.edu<mailto:aaf2@po.cwru.edu>; Abhik Das; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Brad Yoder (Bradley.yoder@hsc.utah.edu<mailto:Bradley.yoder@hsc.utah.edu>); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: REF: Oxygen Saturation Goals

Hey, Wally, a tour de force! Congratulations and thanks for all your hard work in conducting this landmark study and preparing a concise, well written manuscript Some comments—some of which didn't occur to me before--about a few things that in my view remain to be addressed. The only comment likely to be controversial is the last one (which will be relevant to Neil's paper as well). .

1. Typos: Table 2 Pg. 26, you don't want an asterisk (limited to infants alive at 36 weeks) beside BPD (O2 use) or death at 36 weeks or beside BPD (physiologic) or death at 36 weeks. In the middle of page 20, I believe you deleted the word "birth" at the end of sentence (...oxygen restriction started soon after ...). The figure 1 that I received in your manuscript

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(page 31) is for Neil's study. Though a relatively minor issue, it isn't clear why SE rather than SDs are shown in Table 2 (we have provided SDs using similar statistical methods in other trials, right?

2. Power is not actually specified (pg. 16). Although the number of patients enrolled was based on both outcomes and a desire to assess impairment at follow-up, you will want in this trial as for other Network trials to specify the power for the primary outcome of this study (which I anticipate will further strengthen the manuscript and its appeal to the NEJM).

3. Provide the p value for the interaction and add to the appendix a table that provides the rate of the primary outcome in each of the four treatment cells. This can be very easily done. As noted in standards for factorial designs, "accurate interpretation of factorial trials depends on the transparent reporting of data for each treatment cell' (McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials. A systematic review JAMA 2003; 289:2545-2553.) A point often not understand by clinicians is that there can be clinically important effects of using two interventions together even in the absence of a statistical interaction. Such effects can be suggested by providing the outcomes for each cell of these tables. (See comment about using interaction ratios and calculations in Table 6 in the reference above). After reading this you may agree that it would be good with the results you happened to obtain to also add such tables to the appendix for death and for severe ROP.

4. The percent time spent within the oxygen saturation goal range for each group while receiving supplemental oxygen (is this what "present time in actually oxygen saturation range 84-96%" in the last line of Appendix Table 2 is intended to represent?) is a process measure that would be of broad interest to the readers and good to specify in the manuscript. (While the values may be lower that what we would hope for, the number represents what is currently realistic, given the instability of the infants, the nursing ratios achieved in current neonatal units, and the lack of a safe, reliable, and effective servo mechanism for adjusting FiO2 to avoid wide swings in oxygen saturation).

5. Readers may infer that neonatal units can not reduce severe ROP without increasing mortality. However, given the time outside of goal ranges, this would not necessarily be the case if we could find ways to adjust FiO2 and regulate oxygen saturation more precisely. Do you want to say anything in the Discussion about this issue?

6. You fully intended for the diagnosis of BPD by oxygen administration to be based on oxygen administration after the infant was taken off the study oximeter and his/her FIO2 was regulated as under nonstudy conditions. However, for reasons explained below, Georgia indicates that this is not what happened in Houston and perhaps multiple other centers. The study oximeter was removed at 36 weeks 1 day, and BPD by oxygen administration here represents the use of oxygen while the study oximeter was used on day 36 weeks 0 days. Of course, this would not affect the primary outcome but would produce an ascertainment bias increasing the proportion of infants in the high sat arm who had the outcomes of "death or BPD by oxygen administration" and "BPD by oxygen administration". (I think it would have little, probably trivial effect on BPD by physiologic definition which prior to study was given greater emphasis in the study protocol for reasons that Michele has documented)

The above procedure used in Houston because

* The MOP notes that the study oximeter is to be used through 36 weeks
* BPD by oxygen supplementation at 36 weeks was understood to be based on item, A6 on the NG07. The definitions for this item refer oxygen use on the day of 36 weeks postmenstrual age (e.g. as noted on page 5-3 GDB manual of operations Revised May 1, 2008). We understand this day to be the day that the infant is 36 weeks 0 days, and Georgia indicates that the audits have used 36 weeks 0 days).

In my view, we should find out what was done in other units. Perhaps Houston is the only one. In any case I see this as a minor problem that doesn't detract from the primary purpose of the study. However, we would want to acknowledge this limitation, partly because one of the BPD outcomes was significantly lower in the low sat group and because our results are likely to be added to meta-analyses from other studies. I apologize that I didn't recognize this as a problem before or during the study.

Again, Wally, congratulations on a wonderful study and thanks for all the work you have done! You have advanced the field.

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Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

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Sent: Monday, November 30, 2009 3:42 PM
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Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutesof Health
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"; "nfiner@ucsd.edu"
Subject: Re: Oxygen Saturation Goals
Date: Tuesday, December 01, 2009 5:14:38 PM

The email with the papers was really "informational.". I have my blackberry as I am travelling and didn't realize the "reply all" was hit. I would simply let folks know that the papers were submitted.

Thanks
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>
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3. Provide the p value for the interaction and add to the appendix a table that provides the rate of the primary outcome in each of the four treatment cells. This can be very easily done. As noted in standards for factorial designs, "accurate interpretation of factorial trials depends on the transparent reporting of data for each treatment cell' (McAlister FA, Straus SE, Sackett DL,

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Altman DG. Analysis and reporting of factorial trials. A systematic review JAMA 2003; 289:2545-2553.) A point often not understand by clinicians is that there can be clinically important effects of using two interventions together even in the absence of a statistical interaction. Such effects can be suggested by providing the outcomes for each cell of these tables. (See comment about using interaction ratios and calculations in Table 6 in the reference above). After reading this you may agree that it would be good with the results you happened to obtain to also add such tables to the appendix for death and for severe ROP.

4. The percent time spent within the oxygen saturation goal range for each group while receiving supplemental oxygen (is this what "present time in actually oxygen saturation range 84-96%" in the last line of Appendix Table 2 is intended to represent?) is a process measure that would be of broad interest to the readers and good to specify in the manuscript. (While the values may be lower that what we would hope for, the number represents what is currently realistic, given the instability of the infants, the nursing ratios achieved in current neonatal units, and the lack of a safe, reliable, and effective servo mechanism for adjusting FiO2 to avoid wide swings in oxygen saturation).
5. Readers may infer that neonatal units can not reduce severe ROP without increasing mortality. However, given the time outside of goal ranges, this would not necessarily be the case if we could find ways to adjust FiO2 and regulate oxygen saturation more precisely. Do you want to say anything in the Discussion about this issue?
6. You fully intended for the diagnosis of BPD by oxygen administration to be based on oxygen administration after the infant was taken off the study oximeter and his/her FIO2 was regulated as under nonstudy conditions. However, for reasons explained below, Georgia indicates that this is not what happened in Houston and perhaps multiple other centers. The study oximeter was removed at 36 weeks 1 day, and BPD by oxygen administration here represents the use of oxygen while the study oximeter was used on day 36 weeks 0 days. Of course, this would not affect the primary outcome but would produce an ascertainment bias increasing the proportion of infants in the high sat arm who had the outcomes of "death or BPD by oxygen administration" and "BPD by oxygen administration". (I think it would have little, probably trivial effect on BPD by physiologic definition which prior to study was given greater emphasis in the study protocol for reasons that Michele has documented)

   The above procedure used in Houston because

   1. The MOP notes that the study oximeter is to be used through 36 weeks
   2. BPD by oxygen supplementation at 36 weeks was understood to be based on item, A6 on the NG07. The definitions for this item refer oxygen use on the day of 36 weeks postmenstrual age (e.g. as noted on page 5-3 GDB manual of operations Revised May 1, 2008). We understand this day to be the day that the infant is 36 weeks 0 days, and Georgia indicates that the audits have used 36 weeks 0 days).

   In my view, we should find out what was done in other units. Perhaps Houston is the only one. In any case I see this as a minor problem that doesn't detract from the primary purpose of the study. However, we would want to acknowledge this limitation, partly because one of the BPD outcomes was significantly lower in the low sat group and because our results are likely to be added to meta-analyses from other studies. I apologize that I didn't recognize this as a problem before or during the study.

Again, Wally, congratulations on a wonderful study and thanks for all the work you have done! You have advanced the field.

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Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 30, 2009 3:42 PM
To: Rich, Wade; Gantz, Marie; 'Poole Kenneth (E-mail)'; 'Nancy Newman'; Ambal (ambal@uab.edu); Anthony Piazza; 'Susie Buchter'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; 'Brenda Morris'; 'Laroia, Nirupama'; Phelps, Dale; sduara@miami.edu; 'Sood, Beena'; 'Michael O`Shea'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: Confidential SUPPORT papers for submission to NEJM

Hi
Attached are the two SUPPORT papers for submission to NEJM. They will be submitted later this week.

Thanks to everyone for the **quick work in writing the papers** and the **patience and endurance** to conduct this important trial!!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
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301-496-5575

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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"; "nfiner@ucsd.edu"; "wrich@ucsd.edu"
Subject: Re: Confidential SUPPORT papers for submission to NEJM
Date: Tuesday, December 01, 2009 4:26:11 PM

This is correct

Thank
Rose

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Tue Dec 01 14:40:39 2009
Subject: RE: Confidential SUPPORT papers for submission to NEJM

As I understand, the style we are using is to put on the boiler plate
only those who are not authors.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 01, 2009 1:29 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Our boilerplate has Ambal on it - it does not have YOU from Alabama nor
me
from UCSD.
Do we need to add you to the BOILER PLATE for Alabama?? I am fine as is.
Neil

On 12/1/09 10:07 AM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

> Ok.
>
> Neil:
>
> Did you notice that the boiler plate (at least mine) is missing Ambal
as
> an author and is missing disclosures of several authors?
>
> Wally Carlo, M.D.

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> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Tuesday, December 01, 2009 12:03 PM
> To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Yes
>
> ----- Original Message -----
> From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E];
> Rich, Wade <wrich@ucsd.edu>
> Sent: Tue Dec 01 12:40:02 2009
> Subject: RE: Confidential SUPPORT papers for submission to NEJM
>
> Neil and Rose:
>
> Yes, I a, ok. Can we do it today?
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b)
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, December 01, 2009 11:28 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Hi Rose
> I already made that change
> Wally are you OK to submit??
> Neil
>
>
> On 12/1/09 9:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]"

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> <higginsr@mail.nih.gov> wrote:
>
>> The papers are in clearance. If you both are ok with potential
> suggestions
>> after submission for nichd, they can be submitted today. Usually,
> nichd
>> suggestions are minor in nature and are suggestions.
>> Neil- can you make sre we have the correct cincinnati authors (ed +
> vivek)?
>>
>> Once submitted, send me the pdf's.
>>
>> Thanks for all the effort!!
>>
>> Rose
>>
>> ----- Original Message -----
>> From: Finer, Neil <nfiner@ucsd.edu>
>> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
> <wcarlo@peds.uab.edu>
>> Sent: Tue Dec 01 11:44:05 2009
> Subject: FW: Confidential SUPPORT papers for
>> submission to NEJM
>>
>> Hi Rose
>> Are we going to continue to get edits of this detail??
>> I think this process is not helpful. The journal needs to get the
> paper as
>> we have all agreed that if they accept it they will make substantive
>> changes.
>> If we get 23 more inputs some will cancel each other and none will
> change
>> our message.
>> I realize that The NRN has its processes - but I believe we are
> wasting
>> valuable time.
>> Who will actually decide when we can submit what??
>> Wally and I have tried diligently to get these papers ready in the
> shortest
>> time frame so that we could get our message out there.
>> I fully expect J Tyson to have a full list if edits as well.
>> I appreciate your support
>> Neil
>>
>> ------ Forwarded Message
>> From: "Ehrenkranz@Yale. Edu>" <richard.ehrenkranz@yale.edu>
>> Date: Tue, 1 Dec 2009 08:02:51 -0800
>> To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>> Cc: Wade Rich <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, Ken
> Poole
>> <poo@rti.org>, 'Nancy Newman' <nxs5@case.edu>, "Ambal
(ambal@uab.edu)"
>> <ambal@uab.edu>, Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>,
> 'Susie
>> Buchter' <Susie.Buchter@oz.ped.emory.edu>,
> "'Vivek.Narendran@cchmc.org'"
>> <Vivek.Narendran@cchmc.org>, "'vineet.bhandari@yale.edu'"

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>> <vineet.bhandari@yale.edu>, 'Brenda Morris' (b) (6)
> "'Laroia,
>> Nirupama'" <Nirupama_Laroia@URMC.Rochester.edu>, Dale Phelps
>> <Dale_Phelps@URMC.Rochester.edu>, Shahnaz Duara <sduara@miami.edu>,
> "'Sood,
>> Beena'" <bsood@med.wayne.edu>, 'Michael O`Shea' <moshea@wfubmc.edu>,
> Neil
>> Finer <nfiner@ucsd.edu>, "(Luc.Brion@UTSouthwestern.edu)"
>> <Luc.Brion@UTSouthwestern.edu>, "(rohls@unm.edu)" <rohls@unm.edu>, Av
>> Fanaroff <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>,
> "alaptook@WIHRI.org"
>> <alaptook@WIHRI.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)"
>> <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>,
> Wally
>> Carlo <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu"
> <cotte010@mc.duke.edu>,
>> Dennis Wallace <dwallace@rti.org>, Edward Bell
> <edward-bell@uiowa.edu>, Ed
>> Donovan <edward.donovan@cchmc.org>, "Ivan Frantz
>> (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>,
>> "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi
> Watterberg
>> <kwatterberg@salud.unm.edu>, "Kurt Schibler
[kurt.schibler@cchmc.org]"
>> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
> MIckey
>> Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
>> <william_oh@brown.edu>, Pablo Sanchez
> <Pablo.Sanchez@UTSouthwestern.edu>,
>> Roger Faix <Roger.Faix@hsc.utah.edu>, "Duke. Edu>;"
> <goldb008@mc.duke.edu>,
>> Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
>> <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
>> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson
<Jon.E.Tyson@uth.tmc.edu>,
>> "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
>> (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'"
>> <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>
>> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>>
>> Hi:
>> I would like to add my congratulations on a great job by the 2 main
>> writing groups of these manuscripts. I think both manuscripts are
>> extremely tightly written and offer clinically important conclusions.
> I
>> found several typos and have several queries for consideration:
>>
>> CPAP vs surfactant paper:
>> 1.Introduction, paragraph 1, sentence 3-Insert "has" after
> "Surfactant"
>> so that it reads "Surfactant has..."
>> 2. Methods, Statistical analyses: I found the following sentence
>> confusing. "The denominator used to calculate the rate of each
> outcome
>> was the number of infants for whom that outcome was known." Doesn't
> the
>> denominator usually include all patients randomized into each study

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> arm
>> in intent-to-treat analyses? In Table 3, the primary outcomes include
>> all randomized patients in the denominator. When a different number
> was
>> used (eg Total LOS any hospital), it is explained in the footnote. So
> I
>> question whether this sentence is needed.
>> 3. Discussion, paragraph 4, sentence 4: Delete the word "the" before
>> "primary, so that the sentence reads "Both arms of the study were
>> adequately powered for both primary outcomes."
>> 4. Discussion , last paragraph, last sentence: I think that it should
> be
>> "represent" instead of "represents"?
>> 5. "Postnatal" and "postmenstrual" can be used instead of "post natal"
>> and "post menstrual". That will save a few words.
>>
>> SpO2 paper:
>> 1.Abstract, Methods, sentence 2: Delete the comma between threshold
> and
>> retinopathy in the parenthetical phrase.
>> 2. Methods, Enrollment and treatment section, 4th sentence from end of
>> paragraph: Delete hyphen from "post-menstrual" to be consistent
>> throughout paper.
>> 3. Methods, Statistical analyses: See comment #2 above.
>> 4. Table 1: Similar to the CPAP paper, is it possible to include the
> GA
>> strata and the randomization to CPAP vs early intubation by GA strata
> in
>> this Table?
>>
>> Again, congratulations on a great job! I hope that the NEJM agrees!
>> Richard
>>
>>
>> Higgins, Rosemary (NIH/NICHD) [E] wrote:
>>>
>>> Hi
>>>
>>> Attached are the two SUPPORT papers for submission to NEJM. They
> will
>>> be submitted later this week.
>>>
>>>
>>>
>>> Thanks to everyone for the *quick work in writing the papers* and the
>>> *patience and endurance* to conduct this important trial!!!
>>>
>>>
>>>
>>> Rose
>>>
>>>

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>>>
>>> Rosemary D. Higgins, MD
>>>
>>> Program Scientist for the Neonatal Research Network
>>>
>>> Pregnancy and Perinatology Branch
>>>
>>> Center for Developmental Biology and Perinatal Medicine
>>>
>>> Eunice Kennedy Shriver National Institute of Child Health and Human
>>> Development
>>>
>>> National Institutesof Health
>>>
>>> 6100 Executive Blvd., Room 4B03
>>>
>>> MSC 7510
>>>
>>> Bethesda, MD 20892
>>>
>>> For overnight delivery use Rockville, MD 20852
>>>
>>> 301-496-5575
>>>
>>> 301-496-3790 (FAX)
>>>
>>> higginsr@mail.nih.gov
>>>
>>>
>>>
>

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From: Hewitt, Tyl (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: It"s me again -- Oxygen saturation paper.
Date: Tuesday, December 01, 2009 3:41:15 PM

Rose – Sorry for bothering you again but something is not very clear to me in this paper with regard to figure 2. In the text (b) (5) [redacted]

Aren't these two statements looking (b) (5) [redacted] Perhaps what is written on page 19 needs to be expanded/clarified.

We can talk about this one when you get back.

Tyl

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics
and Teratology Branch
Center for Developmental Biology
and Perinatal Medicine
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

Phone: 301-496-5543
FAX: 301-480-0303
E-Mail: hewittt@mail.nih.gov

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From: Hewitt, Tyl (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Early CPAP vs. surfactant paper
Date: Tuesday, December 01, 2009 3:00:37 PM

Perhaps the authors of the CPAP vs. surfactant paper might consider adding verbiage as the authors of the oxygen saturation paper regarding the use of (b) (5) [redacted] – just in case some gomboon like me decides to read the paper.....

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics
and Teratology Branch
Center for Developmental Biology
and Perinatal Medicine
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

Phone: 301-496-5543
FAX: 301-480-0303
E-Mail: hewittt@mail.nih.gov

From: Hewitt, Tyl (NIH/NICHD) [E]
Sent: Tuesday, December 01, 2009 1:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Early CPAP vs. surfactant paper

Then why bother to have (b) (5) [redacted]

Sometimes I don't know why I even bother.....

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics
and Teratology Branch
Center for Developmental Biology
and Perinatal Medicine
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

Phone: 301-496-5543
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 01, 2009 1:17 PM
To: Hewitt, Tyl (NIH/NICHD) [E]
Subject: RE: Early CPAP vs. surfactant paper

Tyl
(b) (5) [redacted] You are not the first to ask about this). NEJM always requires the protocol for publication. All of the outcomes you cite are "secondary" outcomes. (b) (5) [redacted]

Thanks for all your help

Rose
Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hewitt, Tyl (NIH/NICHD) [E]
Sent: Tuesday, December 01, 2009 12:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Early CPAP vs. surfactant paper

And while we're at it, I thought the discussion of the (b) (5) [redacted]

By the way, the previous sentence indicates a (b) (5) [redacted]

I'll send it forward with my comments.

Sorry for being more than a little confused.....

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics

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and Teratology Branch
Center for Developmental Biology
and Perinatal Medicine
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

Phone: 301-496-5543
FAX: 301-480-0303
E-Mail: hewittt@mail.nih.gov

From: Hewitt, Tyl (NIH/NICHD) [E]
Sent: Tuesday, December 01, 2009 12:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Early CPAP vs. surfactant paper

I have a perhaps not too minor a question – but not major either.

Looking at the strata results for (b) (5) [redacted] [Or am I missing something?]

My question is should the (b) (5) [redacted]? Or doesn't it really matter?

Also, would it be meaningful to state in both of the strata that the use of (b) (5) [redacted] Just a thought.....

Have fun in Iowa.

Tyl

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics
and Teratology Branch
Center for Developmental Biology
and Perinatal Medicine
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

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Higgins, Rosemary (NIH/NICHD) [E]

From: Rich, Wade <wrich@ucsd.edu>
Sent: Tuesday, December 01, 2009 2:22 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Ambal is in both our authors and our Boilerplate.
wade

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, December 01, 2009 10:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Ok.

Neil:

Did you notice that the boiler plate (at least mine) is missing Ambal as an author and is missing disclosures of several authors?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, December 01, 2009 12:03 PM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Yes

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Tue Dec 01 12:40:02 2009
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Neil and Rose:

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Yes, I a, ok. Can we do it today?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 01, 2009 11:28 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Hi Rose
I already made that change
Wally are you OK to submit??
Neil

On 12/1/09 9:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> The papers are in clearance. If you both are ok with potential
suggestions
> after submission for nichd, they can be submitted today. Usually,
nichd
> suggestions are minor in nature and are suggestions.
> Neil- can you make sre we have the correct cincinnati authors (ed +
vivek)?
>
> Once submitted, send me the pdf's.
>
> Thanks for all the effort!!
>
> Rose
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
<wcarlo@peds.uab.edu>
> Sent: Tue Dec 01 11:44:05 2009
Subject: FW: Confidential SUPPORT papers for

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> submission to NEJM
>
> Hi Rose
> Are we going to continue to get edits of this detail??
> I think this process is not helpful. The journal needs to get the paper as
> we have all agreed that if they accept it they will make substantive
> changes.
> If we get 23 more inputs some will cancel each other and none will change
> our message.
> I realize that The NRN has its processes - but I believe we are wasting
> valuable time.
> Who will actually decide when we can submit what??
> Wally and I have tried diligently to get these papers ready in the shortest
> time frame so that we could get our message out there.
> I fully expect J Tyson to have a full list if edits as well.
> I appreciate your support
> Neil
>
> ------ Forwarded Message
> From: "Ehrenkranz@Yale. Edu>" <richard.ehrenkranz@yale.edu>
> Date: Tue, 1 Dec 2009 08:02:51 -0800
> To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
> Cc: Wade Rich <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, Ken Poole
> <poo@rti.org>, 'Nancy Newman' <nxs5@case.edu>, "Ambal (ambal@uab.edu)"
> <ambal@uab.edu>, Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>, 'Susie
> Buchter' <Susie.Buchter@oz.ped.emory.edu>, "'Vivek.Narendran@cchmc.org'"
> <Vivek.Narendran@cchmc.org>, "'vineet.bhandari@yale.edu'"
> <vineet.bhandari@yale.edu>, 'Brenda Morris' (b) (6) "'Laroia,
> Nirupama'" <Nirupama_Laroia@URMC.Rochester.edu>, Dale Phelps
> <Dale_Phelps@URMC.Rochester.edu>, Shahnaz Duara <sduara@miami.edu>, "'Sood,
> Beena'" <bsood@med.wayne.edu>, 'Michael O`Shea' <moshea@wfubmc.edu>, Neil
> Finer <nfiner@ucsd.edu>, "(Luc.Brion@UTSouthwestern.edu)"
> <Luc.Brion@UTSouthwestern.edu>, "(rohls@unm.edu)" <rohls@unm.edu>, Av
> Fanaroff <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>, "alaptook@WIHRI.org"
> <alaptook@WIHRI.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)"
> <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>, Wally
> Carlo <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>,
> Dennis Wallace <dwallace@rti.org>, Edward Bell <edward-bell@uiowa.edu>, Ed

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> Donovan <edward.donovan@cchmc.org>, "Ivan Frantz
> (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>,
> "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi
Watterberg
> <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]"
> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
MIckey
> Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
> <william_oh@brown.edu>, Pablo Sanchez
<Pablo.Sanchez@UTSouthwestern.edu>,
> Roger Faix <Roger.Faix@hsc.utah.edu>, "Duke. Edu>;"
<goldb008@mc.duke.edu>,
> Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
> <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu>,
> "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
> (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'"
> <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Hi:
> I would like to add my congratulations on a great job by the 2 main
> writing groups of these manuscripts. I think both manuscripts are
> extremely tightly written and offer clinically important conclusions.
I
> found several typos and have several queries for consideration:
>
> CPAP vs surfactant paper:
> 1.Introduction, paragraph 1, sentence 3-Insert "has" after
"Surfactant"
> so that it reads "Surfactant has..."
> 2. Methods, Statistical analyses: I found the following sentence
> confusing. "The denominator used to calculate the rate of each
outcome
> was the number of infants for whom that outcome was known." Doesn't
the
> denominator usually include all patients randomized into each study
arm
> in intent-to-treat analyses? In Table 3, the primary outcomes include
> all randomized patients in the denominator. When a different number
was
> used (eg Total LOS any hospital), it is explained in the footnote. So
I
> question whether this sentence is needed.
> 3. Discussion, paragraph 4, sentence 4: Delete the word "the" before
> "primary, so that the sentence reads "Both arms of the study were
> adequately powered for both primary outcomes."
> 4. Discussion , last paragraph, last sentence: I think that it should
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> "represent" instead of "represents"?
> 5. "Postnatal" and "postmenstrual" can be used instead of "post natal"
> and "post menstrual". That will save a few words.

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>
> SpO2 paper:
> 1.Abstract, Methods, sentence 2: Delete the comma between threshold
and
> retinopathy in the parenthetical phrase.
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> paragraph: Delete hyphen from "post-menstrual" to be consistent
> throughout paper.
> 3. Methods, Statistical analyses: See comment #2 above.
> 4. Table 1: Similar to the CPAP paper, is it possible to include the
GA
> strata and the randomization to CPAP vs early intubation by GA strata
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>
> Again, congratulations on a great job! I hope that the NEJM agrees!
> Richard
>
>
> Higgins, Rosemary (NIH/NICHD) [E] wrote:
>>
>> Hi
>>
>> Attached are the two SUPPORT papers for submission to NEJM. They
will
>> be submitted later this week.
>>
>>
>>
>> Thanks to everyone for the *quick work in writing the papers* and the
>> *patience and endurance* to conduct this important trial!!!
>>
>>
>>
>> Rose
>>
>>
>>
>> Rosemary D. Higgins, MD
>>
>> Program Scientist for the Neonatal Research Network
>>
>> Pregnancy and Perinatology Branch
>>
>> Center for Developmental Biology and Perinatal Medicine
>>
>> Eunice Kennedy Shriver National Institute of Child Health and Human
>> Development
>>
>> National Institutesof Health
>>
>> 6100 Executive Blvd., Room 4B03

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>>
>> MSC 7510
>>
>> Bethesda, MD 20892
>>
>> For overnight delivery use Rockville, MD 20852
>>
>> 301-496-5575
>>
>> 301-496-3790 (FAX)
>>
>> higginsr@mail.nih.gov
>>
>>
>>

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, December 01, 2009 2:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Ambal is author # 10 on the CPAP paper
Neil

On 12/1/09 10:09 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> Ambal should be on both papers; no one reported any conflicts (and we
> had everyone).
>
> Let me know if you need anything else
>
> Rose
>
> ----- Original Message -----
> From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
> <nfiner@ucsd.edu>; wrich@ucsd.edu <wrich@ucsd.edu>
> Sent: Tue Dec 01 13:07:36 2009
Subject: RE: Confidential SUPPORT papers for
> submission to NEJM
>
> Ok.
>
> Neil:
>
> Did you notice that the boiler plate (at least mine) is missing Ambal
> as an author and is missing disclosures of several authors?
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics University of Alabama at
> Birmingham Director, Division of Neonatology Director, Newborn
> Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Tuesday, December 01, 2009 12:03 PM

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> To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Yes
>
> ----- Original Message -----
> From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E];
> Rich, Wade <wrich@ucsd.edu>
> Sent: Tue Dec 01 12:40:02 2009
> Subject: RE: Confidential SUPPORT papers for submission to NEJM
>
> Neil and Rose:
>
> Yes, I a, ok. Can we do it today?
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics University of Alabama at
> Birmingham Director, Division of Neonatology Director, Newborn
> Nurseries
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>> Neil- can you make sre we have the correct cincinnati authors (ed +
> vivek)?
>>

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>> Once submitted, send me the pdf's.
>>
>> Thanks for all the effort!!
>>
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>>
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>> From: "Ehrenkranz@Yale. Edu>" <richard.ehrenkranz@yale.edu>
>> Date: Tue, 1 Dec 2009 08:02:51 -0800
>> To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
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> Poole
>> <poo@rti.org>, 'Nancy Newman' <nxs5@case.edu>, "Ambal (ambal@uab.edu)"
>> <ambal@uab.edu>, Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>,
> 'Susie
>> Buchter' <Susie.Buchter@oz.ped.emory.edu>,
> "'Vivek.Narendran@cchmc.org'"
>> <Vivek.Narendran@cchmc.org>, "'vineet.bhandari@yale.edu'"
>> <vineet.bhandari@yale.edu>, 'Brenda Morris' (b) (6)
> "'Laroia,
>> Nirupama'" <Nirupama_Laroia@URMC.Rochester.edu>, Dale Phelps
>> <Dale_Phelps@URMC.Rochester.edu>, Shahnaz Duara <sduara@miami.edu>,
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> Neil
>> Finer <nfiner@ucsd.edu>, "(Luc.Brion@UTSouthwestern.edu)"
>> <Luc.Brion@UTSouthwestern.edu>, "(rohls@unm.edu)" <rohls@unm.edu>, Av
>> Fanaroff <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>,
> "alaptook@WIHRI.org"
>> <alaptook@WIHRI.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)"
>> <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>,
> Wally
>> Carlo <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu"
> <cotte010@mc.duke.edu>,
>> Dennis Wallace <dwallace@rti.org>, Edward Bell
> <edward-bell@uiowa.edu>, Ed
>> Donovan <edward.donovan@cchmc.org>, "Ivan Frantz
>> (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>,
>> "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi
> Watterberg
>> <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]"
>> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
> MIckey
>> Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
>> <william_oh@brown.edu>, Pablo Sanchez
> <Pablo.Sanchez@UTSouthwestern.edu>,
>> Roger Faix <Roger.Faix@hsc.utah.edu>, "Duke. Edu>;"
> <goldb008@mc.duke.edu>,
>> Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
>> <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
>> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson
>> <Jon.E.Tyson@uth.tmc.edu>, "VanMeurs, Krisa"
>> <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
>> (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'"
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>> include all randomized patients in the denominator. When a different
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>>>
>>>
>>>
>>> Rose
>>>

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>>>
>>>
>>> Rosemary D. Higgins, MD
>>>
>>> Program Scientist for the Neonatal Research Network
>>>
>>> Pregnancy and Perinatology Branch
>>>
>>> Center for Developmental Biology and Perinatal Medicine
>>>
>>> Eunice Kennedy Shriver National Institute of Child Health and Human
>>> Development
>>>
>>> National Institutesof Health
>>>
>>> 6100 Executive Blvd., Room 4B03
>>>
>>> MSC 7510
>>>
>>> Bethesda, MD 20892
>>>
>>> For overnight delivery use Rockville, MD 20852
>>>
>>> 301-496-5575
>>>
>>> 301-496-3790 (FAX)
>>>
>>> higginsr@mail.nih.gov
>>>
>>>
>>>
>

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From: Archer, Stephanie (NIH/NICHD) [E]
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; nfiner@ucsd.edu
Subject: RE: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants
Date: Tuesday, December 01, 2009 1:31:50 PM
Attachments: Carlo, SUPPORT Oxygen Saturation, 2009-12-01 swa.doc

Attached is a revised version with Ambal as an author (I took him out of the boilerplate). I also deleted the table of email addresses -- that shouldn't be included in the paper, but you will likely need the addresses as part of the submission process.

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Tuesday, December 01, 2009 10:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; nfiner@ucsd.edu
Cc: Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]
Subject: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Authors:
Dr. Carlo asked that I send draft #8 to you for your review. Your changes from over the holiday weekend have been made to this draft.

Also, Stephanie and Marie:
I included the broiler plate on this draft (#8) that we received on 11/26/09. I had a few questions about this. 1) Should Namasivayam Ambalavanan be included as an author? and 2) Should we follow the NEJM style for the broilerplate (double space, font, etc.)? Thanks very much.

Marsha

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy S. Newman, RN[3]; Namasivayam Ambalavanan, MD[1]; Ivan D. Frantz III, MD[9]; Pablo J. Sánchez, MD[10]; Anthony J. Piazza, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13] ; Dale L. Phelps, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P. Van Meurs, MD[16]; Shahnaz Duara, MD[17]; Vivek Narendran, MD MRCP[8]; Beena G. Sood, MD MS[18]; T. Michael O'Shea,

[1] Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL
[2] University of California at San Diego, San Diego, CA
[3] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH
[4] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC
[5] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[6] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[8] Department of Pediatrics, University of Cincinnati, Cincinnati, OH
[9] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA
[10] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX
[11] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[12] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[13] University of Rochester Medical Center, Rochester, NY
[14] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN
[15] Department of Pediatrics, Duke University, Durham, NC
[16] Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA
[17] University of Miami Miller School of Medicine, Miami, FL
[18] Department of Pediatrics, Wayne State University, Detroit, MI

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MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23] for the NICHD Neonatal Research Network

[19] Wake Forest University School of Medicine, Winston-Salem, NC
[20] Department of Pediatrics, University of Iowa, Iowa City, IA
[21] Department of Pediatrics, Yale University School of Medicine, New Haven, CT
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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.210). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy or ~~/~~death but resulted in an increase in mortality ~~that~~ and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels ≥ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[1-3,3-5,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of ≥ 92% (3.3 ± 0.3%) or ≥98% (5.6 ± 1.1%) than in units with lower oxygen saturation targets (1.4 ± 0.2% and 3.1 ± 0.3%, respectively).[35] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring

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ablation therapy was 27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these ~~recent prospective observational studies, retrospective studies, or controlled~~ studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ~~the incidence of~~ retinopathy of prematurity, concerns remain about the safety of these oxygen saturation targets~~an increase in serious adverse effects or deaths were not reported~~.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and two ventilation approaches (continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies). The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and at RTI, International~~Research Triangle International~~, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). ~~A similar algorithm was used to~~ A previous trial used a fixed 3% absolute oxygen saturation offset throughout the entire range of saturations to mask caregivers and separate oxygen saturations in premature infants.[17] The algorithm used in the current trial differed markedly as the oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or

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higher than 96% in both treatment groups. ~~Thus, a~~An oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display value of 84% corresponded~~s~~ to actual values of 8~~4~~7 and 84-87% in the low and high target groups, respectively. ~~The oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups.~~ Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting compliance~~performance~~. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

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Research nurses recorded all data using standardized definitions included in the trial's Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmologists~~ical~~ trained in the diagnosis of ~~specialists familiar with~~ retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following occurred~~were present~~: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death.

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Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

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Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the ~~46~~ planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on ~~36~~ pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

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RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.210; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one

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year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was considerable~~substantial~~ overlap (Figure 3). These data indicated that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome.

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Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The increase in mortality in the current trial may be related either to the lower oxygen saturation targets or the use of oxygen restriction started soon after birth.~~from birth in the current trial may be related to the adverse outcome.~~

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[6,23] There have not been other randomized controlled trials of different oxygen targeting begun ~~starting~~ soon

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after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.32)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk[†] (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value[§]
Length of stay any hospital, (days) m±SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m±SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m±SE[†]	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m±SE[†]	59.8 ± 1.6	67.4 ± 1.5	<0.001
Continuous positive airway pressure, (days) m±SE[†]	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m±SE[†]	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27
Precent of time in actual oxygen saturation range 84-96%, (%) m±SD‡	66.9 ± 13.9	68.0 ± 15.2	0.16¶

*Among survivors to discharge, transfer or one year; maximum value is 366 days

[†]Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Percent of time based only on total time on oxygen supplementation

§Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

¶Unadjusted P value

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes severe retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks. The question marks in the ROP outcome boxes are for infants in whom the final ROP outcome could not be ascertained because of loss to follow up.

Figure 2. ~~Survival curve~~Survivor curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. ~~The median oxygen saturations were significantly lower for infants in the 85 to 89% oxygen saturation target group.~~ The medians of the distributions were significantly different based on a Rank Sums test ($p < 0.001$).

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Figure 1.

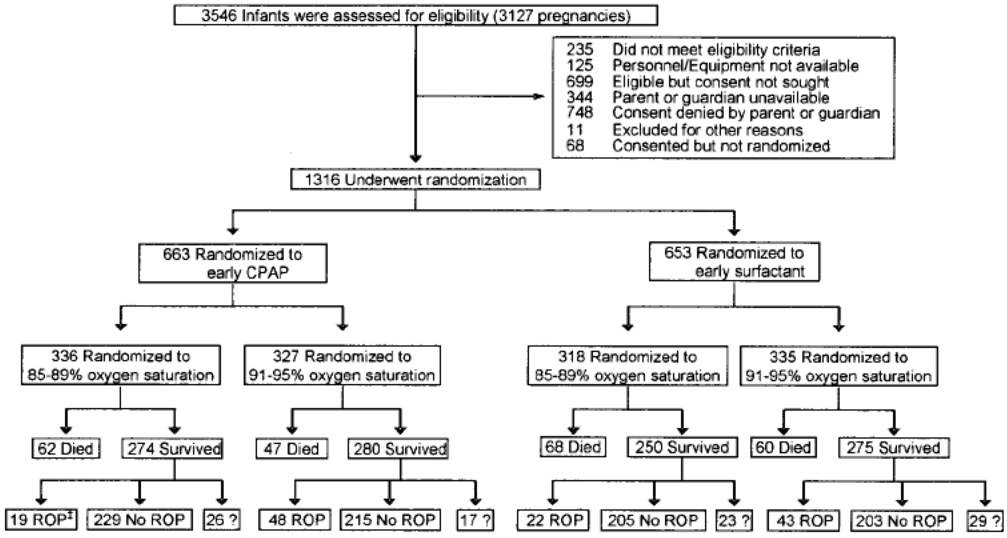

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Figure 2. Survivor Curve for Mortality

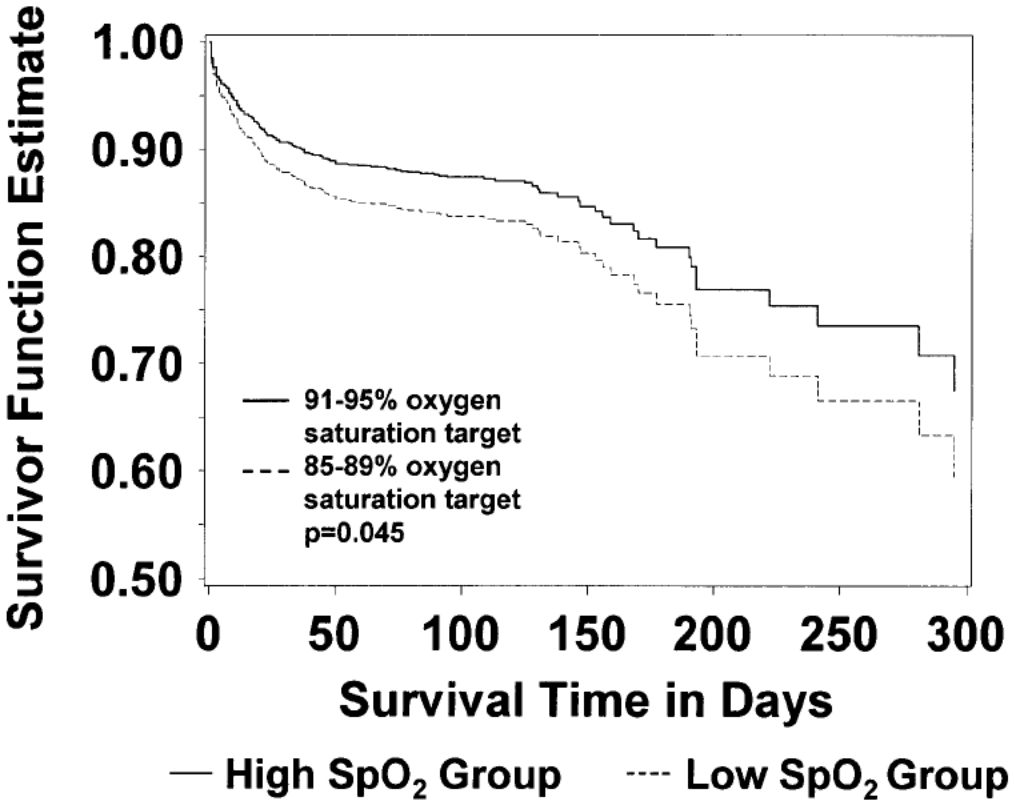

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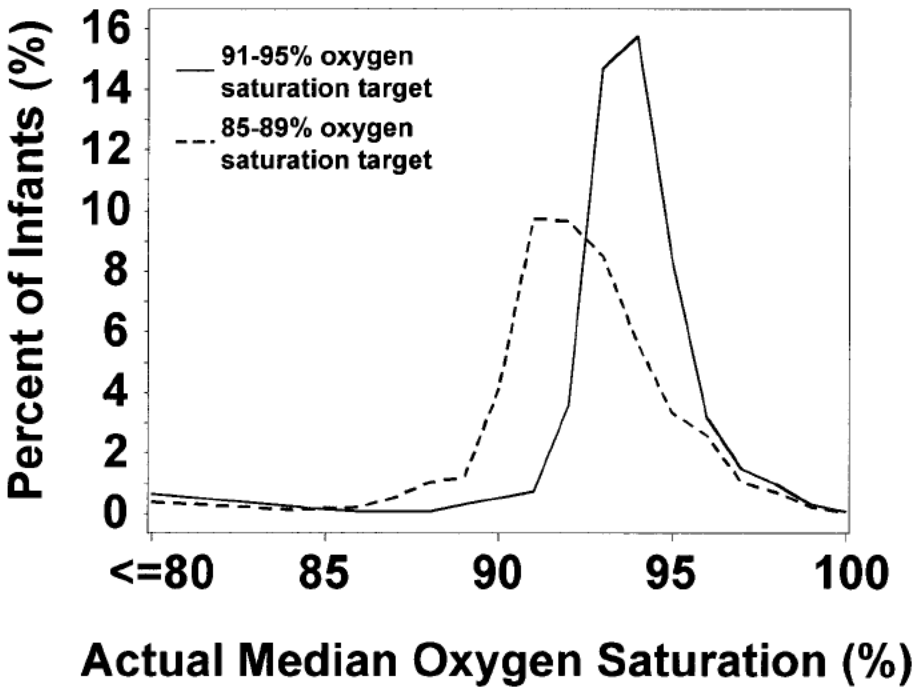
Figure 3.



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to thee conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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3. Anderson G, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: A national survey of recent practices. J Perinatol 2004;24:164-8.

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4. Deulofeut R, Sola A. Treatment-by-gender effect when aiming to avoid hyperoxia in preterm infants in the NICU. Acta Paediatr 2007;96:990-4.

5. Wright KW, Thompson SD, Ramanathan R, Joseph R, Farzavandi S. A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. Trans Am Ophthalmol Soc 2006;104:78-84.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wrich@ucsd.edu"
Subject: Re: Confidential SUPPORT papers for submission to NEJM
Date: Tuesday, December 01, 2009 1:26:42 PM

---

susie.buchter@oz.ped.emory.edu

----- Original Message -----
From: Rich, Wade <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Dec 01 13:24:47 2009
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Susan Buchter does not have an email on Network site, and is not in our email string. What is her email and I assume she is from Emory?
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, December 01, 2009 10:10 AM
To: 'wcarlo@peds.uab.edu'; Finer, Neil; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Ambal should be on both papers; no one reported any conflicts (and we had everyone).

Let me know if you need anything else

Rose

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; wrich@ucsd.edu <wrich@ucsd.edu>
Sent: Tue Dec 01 13:07:36 2009
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Ok.

Neil:

Did you notice that the boiler plate (at least mine) is missing Ambal as an author and is missing disclosures of several authors?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
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Birmingham, AL 35233-7335
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, December 01, 2009 12:03 PM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Yes

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Tue Dec 01 12:40:02 2009
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Neil and Rose:

Yes, I a, ok. Can we do it today?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 01, 2009 11:28 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Hi Rose
I already made that change
Wally are you OK to submit??
Neil

On 12/1/09 9:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> The papers are in clearance. If you both are ok with potential
suggestions
> after submission for nichd, they can be submitted today. Usually,
nichd
> suggestions are minor in nature and are suggestions.
> Neil- can you make sre we have the correct cincinnati authors (ed +
vivek)?
>
> Once submitted, send me the pdf's.
>

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> Thanks for all the effort!!
>
> Rose
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
<wcarlo@peds.uab.edu>
> Sent: Tue Dec 01 11:44:05 2009
Subject: FW: Confidential SUPPORT papers for
> submission to NEJM
>
> Hi Rose
> Are we going to continue to get edits of this detail??
> I think this process is not helpful. The journal needs to get the
paper as
> we have all agreed that if they accept it they will make substantive
> changes.
> If we get 23 more inputs some will cancel each other and none will
change
> our message.
> I realize that The NRN has its processes - but I believe we are
wasting
> valuable time.
> Who will actually decide when we can submit what??
> Wally and I have tried diligently to get these papers ready in the
shortest
> time frame so that we could get our message out there.
> I fully expect J Tyson to have a full list if edits as well.
> I appreciate your support
> Neil
>
> ------ Forwarded Message
> From: "Ehrenkranz@Yale. Edu>" <richard.ehrenkranz@yale.edu>
> Date: Tue, 1 Dec 2009 08:02:51 -0800
> To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
> Cc: Wade Rich <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, Ken
Poole
> <poo@rti.org>, 'Nancy Newman' <nxs5@case.edu>, "Ambal (ambal@uab.edu)"
> <ambal@uab.edu>, Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>,
'Susie
> Buchter' <Susie.Buchter@oz.ped.emory.edu>,
"'Vivek.Narendran@cchmc.org'"
> <Vivek.Narendran@cchmc.org>, "'vineet.bhandari@yale.edu'"
> <vineet.bhandari@yale.edu>, 'Brenda Morris' (b) (6)
"'Laroia,
> Nirupama'" <Nirupama_Laroia@URMC.Rochester.edu>, Dale Phelps
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> Fanaroff <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>,
"alaptook@WIHRI.org"
> <alaptook@WIHRI.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)"
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> "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi
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> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
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> Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
> <william_oh@brown.edu>, Pablo Sanchez
<Pablo.Sanchez@UTSouthwestern.edu>,
> Roger Faix <Roger.Faix@hsc.utah.edu>, "Duke. Edu>;"
<goldb008@mc.duke.edu>,
> Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
> <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu>,
> "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
> (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter, Kristin'"
> <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Hi:
> I would like to add my congratulations on a great job by the 2 main
> writing groups of these manuscripts. I think both manuscripts are
> extremely tightly written and offer clinically important conclusions.
I
> found several typos and have several queries for consideration:
>
> CPAP vs surfactant paper:
> 1.Introduction, paragraph 1, sentence 3-Insert "has" after
"Surfactant"
> so that it reads "Surfactant has..."
> 2. Methods, Statistical analyses: I found the following sentence
> confusing. "The denominator used to calculate the rate of each
outcome
> was the number of infants for whom that outcome was known." Doesn't
the
> denominator usually include all patients randomized into each study
arm
> in intent-to-treat analyses? In Table 3, the primary outcomes include
> all randomized patients in the denominator. When a different number
was
> used (eg Total LOS any hospital), it is explained in the footnote. So
I
> question whether this sentence is needed.
> 3. Discussion, paragraph 4, sentence 4: Delete the word "the" before
> "primary, so that the sentence reads "Both arms of the study were
> adequately powered for both primary outcomes."
> 4. Discussion , last paragraph, last sentence: I think that it should
be
> "represent" instead of "represents"?
> 5. "Postnatal" and "postmenstrual" can be used instead of "post natal"
> and "post menstrual". That will save a few words.

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>
> SpO2 paper:
> 1.Abstract, Methods, sentence 2: Delete the comma between threshold
and
> retinopathy in the parenthetical phrase.
> 2. Methods, Enrollment and treatment section, 4th sentence from end of
> paragraph: Delete hyphen from "post-menstrual" to be consistent
> throughout paper.
> 3. Methods, Statistical analyses: See comment #2 above.
> 4. Table 1: Similar to the CPAP paper, is it possible to include the
GA
> strata and the randomization to CPAP vs early intubation by GA strata
in
> this Table?
>
> Again, congratulations on a great job! I hope that the NEJM agrees!
> Richard
>
>
> Higgins, Rosemary (NIH/NICHD) [E] wrote:
>>
>> Hi
>>
>> Attached are the two SUPPORT papers for submission to NEJM. They
will
>> be submitted later this week.
>>
>>
>>
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>> *patience and endurance* to conduct this important trial!!!
>>
>>
>>
>> Rose
>>
>>
>>
>> Rosemary D. Higgins, MD
>>
>> Program Scientist for the Neonatal Research Network
>>
>> Pregnancy and Perinatology Branch
>>
>> Center for Developmental Biology and Perinatal Medicine
>>
>> Eunice Kennedy Shriver National Institute of Child Health and Human
>> Development
>>
>> National Institutesof Health
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>> 6100 Executive Blvd., Room 4B03
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>> MSC 7510
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>> Bethesda, MD 20892
>>

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>> For overnight delivery use Rockville, MD 20852
>>
>> 301-496-5575
>>
>> 301-496-3790 (FAX)
>>
>> higginsr@mail.nih.gov
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>>

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, December 01, 2009 1:00 PM
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

I take it from Rose that we can submit today and make any chnges later - There will be plenty of time for those Yes we cam submit today Neil

Sent from my iPhone

On Dec 1, 2009, at 9:47 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
wrote:

> Neil:
>
> Have we had NIH clearance?
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics University of Alabama at
> Birmingham Director, Division of Neonatology Director, Newborn
> Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266(b) (6)
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, December 01, 2009 11:45 AM
> To: Wally Carlo, M.D.
> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>
> Wally
> Go for it
> I am starting the upload
> Neil
>
>
> On 12/1/09 9:40 AM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:
>
>> Neil and Rose:
>>
>> Yes, I a, ok. Can we do it today?

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>>
>> Wally
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>> Cell: 205 266 (b) (6)
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>> -----Original Message-----
>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>> Sent: Tuesday, December 01, 2009 11:28 AM
>> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
>> Subject: Re: Confidential SUPPORT papers for submission to NEJM
>>
>> Hi Rose
>> I already made that change
>> Wally are you OK to submit??
>> Neil
>>
>>
>> On 12/1/09 9:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
>> <higginsr@mail.nih.gov> wrote:
>>
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>> suggestions
>>> after submission for nichd, they can be submitted today. Usually,
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>>> From: Finer, Neil <nfiner@ucsd.edu>
>>> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
>> <wcarlo@peds.uab.edu>
>>> Sent: Tue Dec 01 11:44:05 2009
>> Subject: FW: Confidential SUPPORT papers for
>>> submission to NEJM
>>>
>>> Hi Rose

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>>> I fully expect J Tyson to have a full list if edits as well.
>>> I appreciate your support
>>> Neil
>>>
>>> ------ Forwarded Message
>>> From: "Ehrenkranz@Yale. Edu>" <richard.ehrenkranz@yale.edu>
>>> Date: Tue, 1 Dec 2009 08:02:51 -0800
>>> To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>>> Cc: Wade Rich <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, Ken
>> Poole
>>> <poo@rti.org>, 'Nancy Newman' <nxs5@case.edu>, "Ambal
> (ambal@uab.edu)"
>>> <ambal@uab.edu>, Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>,
>> 'Susie
>>> Buchter' <Susie.Buchter@oz.ped.emory.edu>,
>> "'Vivek.Narendran@cchmc.org'"
>>> <Vivek.Narendran@cchmc.org>, "'vineet.bhandari@yale.edu'"
>>> <vineet.bhandari@yale.edu>, 'Brenda Morris' (b) (6)
>> "'Laroia,
>>> Nirupama'" <Nirupama_Laroia@URMC.Rochester.edu>, Dale Phelps
>>> <Dale_Phelps@URMC.Rochester.edu>, Shahnaz Duara <sduara@miami.edu>,
>> "'Sood,
>>> Beena'" <bsood@med.wayne.edu>, 'Michael O`Shea' <moshea@wfubmc.edu>,
>> Neil
>>> Finer <nfiner@ucsd.edu>, "(Luc.Brion@UTSouthwestern.edu)"
>>> <Luc.Brion@UTSouthwestern.edu>, "(rohls@unm.edu)" <rohls@unm.edu>,
>>> Av Fanaroff <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>,
>> "alaptook@WIHRI.org"
>>> <alaptook@WIHRI.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)"
>>> <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter
>>> <bpoindex@iupui.edu>,
>> Wally
>>> Carlo <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu"
>> <cotte010@mc.duke.edu>,
>>> Dennis Wallace <dwallace@rti.org>, Edward Bell
>> <edward-bell@uiowa.edu>, Ed
>>> Donovan <edward.donovan@cchmc.org>, "Ivan Frantz

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>>> (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>,
>>> "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi
>> Watterberg
>>> <kwatterberg@salud.unm.edu>, "Kurt Schibler
> [kurt.schibler@cchmc.org]"
>>> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
>> MIckey
>>> Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
>>> <william_oh@brown.edu>, Pablo Sanchez
>> <Pablo.Sanchez@UTSouthwestern.edu>,
>>> Roger Faix <Roger.Faix@hsc.utah.edu>, "Duke. Edu>;"
>> <goldb008@mc.duke.edu>,
>>> Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-
>>> mail)"
>>> <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)"
>>> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson
> <Jon.E.Tyson@uth.tmc.edu>,
>>> "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
>>> (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "'Zaterka-Baxter,
>>> Kristin'"
>>> <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>
>>> Subject: Re: Confidential SUPPORT papers for submission to NEJM
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>>> 2. Methods, Enrollment and treatment section, 4th sentence from end
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>>> 3. Methods, Statistical analyses: See comment #2 above.
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Higgins, Rosemary (NIH/NICHD) [E]

From: Rich, Wade <wrich@ucsd.edu>
Sent: Tuesday, December 01, 2009 12:31 PM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Confidential SUPPORT papers for submission to NEJM

Can I submit also? I already made the changes you suggested.
wade

-----Original Message-----
From: Finer, Neil
Sent: Tuesday, December 01, 2009 9:28 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Rich, Wade
Subject: Re: Confidential SUPPORT papers for submission to NEJM

Hi Rose
I already made that change
Wally are you OK to submit??
Neil

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<higginsr@mail.nih.gov> wrote:

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> Frantz (ifrantz@tuftsmedicalcenter.org)"
> <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A"
> <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi Watterberg <kwatterberg@salud.unm.edu>, "Kurt Schibler
[kurt.schibler@cchmc.org]"
> <kurt.schibler@cchmc.org>, Michele Walsh-Sukys <mcw3@po.cwru.edu>,
> MIckey Caplan <mcaplan@northshore.org>, "Oh William (E-mail)"
> <william_oh@brown.edu>, Pablo Sanchez
> <Pablo.Sanchez@UTSouthwestern.edu>,
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> <goldb008@mc.duke.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)"
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> <barbara_stoll@oz.ped.emory.edu>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu>,
> "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>, "Archer, Stephanie
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Confidential SUPPORT papers for submission to NEJM
Date: Tuesday, December 01, 2009 9:57:00 AM
Attachments: Carlo SUPPORT O2 2009-11-25 CLEAN MASTER.doc
SUPPORT Nov 30 Final.doc
NEJM Tables and Figure Nov 30 Final.doc

Here are close to final drafts of the Two SUPPORT papers-
Thanks for all your help, perseverance and financial support for this study!!
Rose

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy S. Newman, RN[3]; Namasivayam Ambalavanan, MD[1]; Ivan D. Frantz III, MD[9]; Pablo J. Sánchez, MD[10]; Anthony J. Piazza, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Dale L. Phelps, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD, MHS[15]; Krisa P. Van Meurs, MD[16]; Shahnaz Duara, MD[17]; Beena G. Sood, MD, MS[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; and Rosemary D. Higgins, MD[23] for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [2]University of California at San Diego, San Diego, CA; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics

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and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]University of Miami Miller School of Medicine, Miami, FL; [18]Department of Pediatrics, Wayne State University, Detroit, MI; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]University of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

Waldemar A. Carlo, M.D.
University of Alabama at Birmingham
525 New Hillman Building
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Birmingham, AL 35233

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Acknowledgements

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.21). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy or death but resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3-5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of $\geq$ 92% (3.3 $\pm$ 0.3%) or $\geq$98% (5.6 $\pm$ 1.1%) than in units with lower oxygen saturation targets (1.4 $\pm$ 0.2% and 3.1 $\pm$ 0.3%, respectively).[5] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was

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27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease retinopathy of prematurity, concerns remain about the safety of these oxygen saturation targets.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and two ventilation approaches (continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies). The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent data coordinating center, approved the trial.

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Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). A previous trial used a fixed 3% absolute oxygen saturation offset throughout the entire range of saturations to mask caregivers and separate oxygen saturations in premature infants.[17] The algorithm used in the current trial differed markedly as the oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups. An oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an

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oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display value of 84% corresponded to actual values of 84 and 84-87% in the low and high target groups, respectively. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting compliance. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial's Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New

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Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following occurred: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and

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gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on 36 pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and

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Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.21; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the

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two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was considerable overlap (Figure 3). These data indicate that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome. Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

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This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The increase in mortality in the current trial may be related either to the lower oxygen saturation targets or the use of oxygen restriction started soon after.

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,23] There have not been other randomized controlled trials of different oxygen targeting begun soon after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for

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oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.3)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk† (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value‡
Length of stay any hospital, (days) m+SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m+SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m+SE†	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m+SE†	59.8 ± 1.6	67.4 ± 1.5	0.0002
Continuous positive airway pressure, (days) m+SE†	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27
Present time in actual oxygen saturation range 84-96%, %	66.9 ± 13.9	68.0 ± 13.9	0.16

*Among survivors to discharge, transfer or one year; maximum value is 366 days

†Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes severe retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks. The question marks in the ROP outcome boxes are for infants in whom the first ROP outcome could not be ascertained because of loss to follow up.

Figure 2. Survivor curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. The medians of the distributions were significantly different based on a Rank Sums test ($p < 0.001$).

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Figure 1.

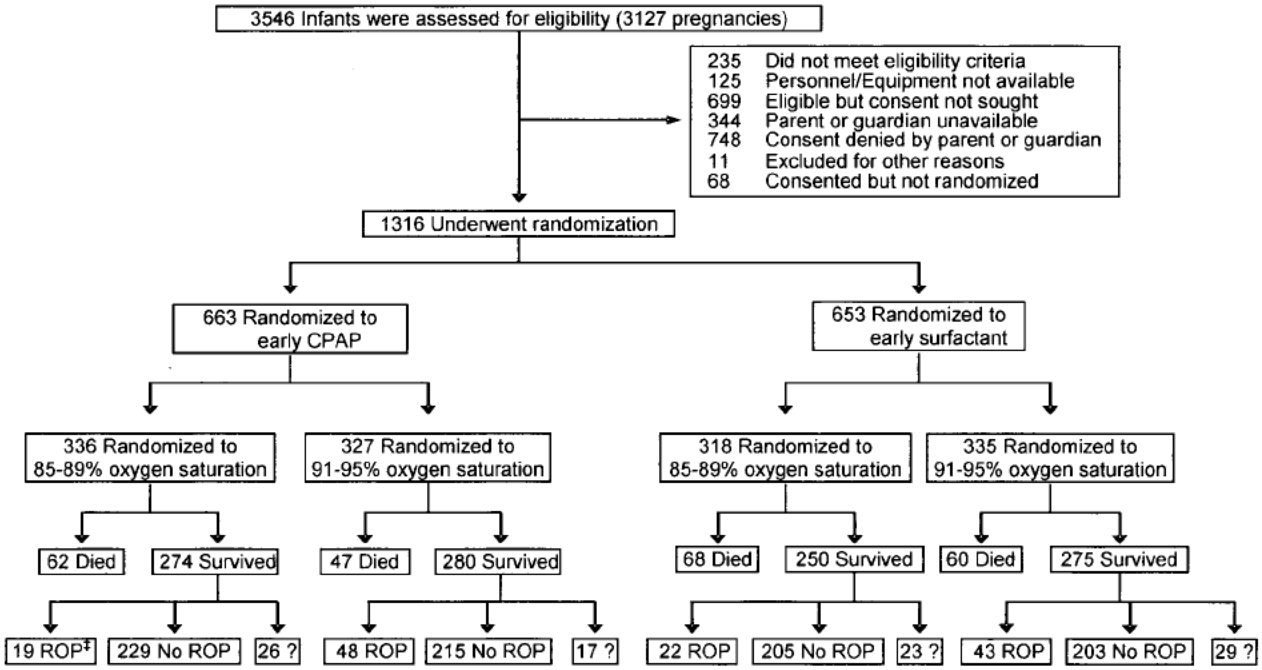

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Figure 2. Survivor Curve for Mortality

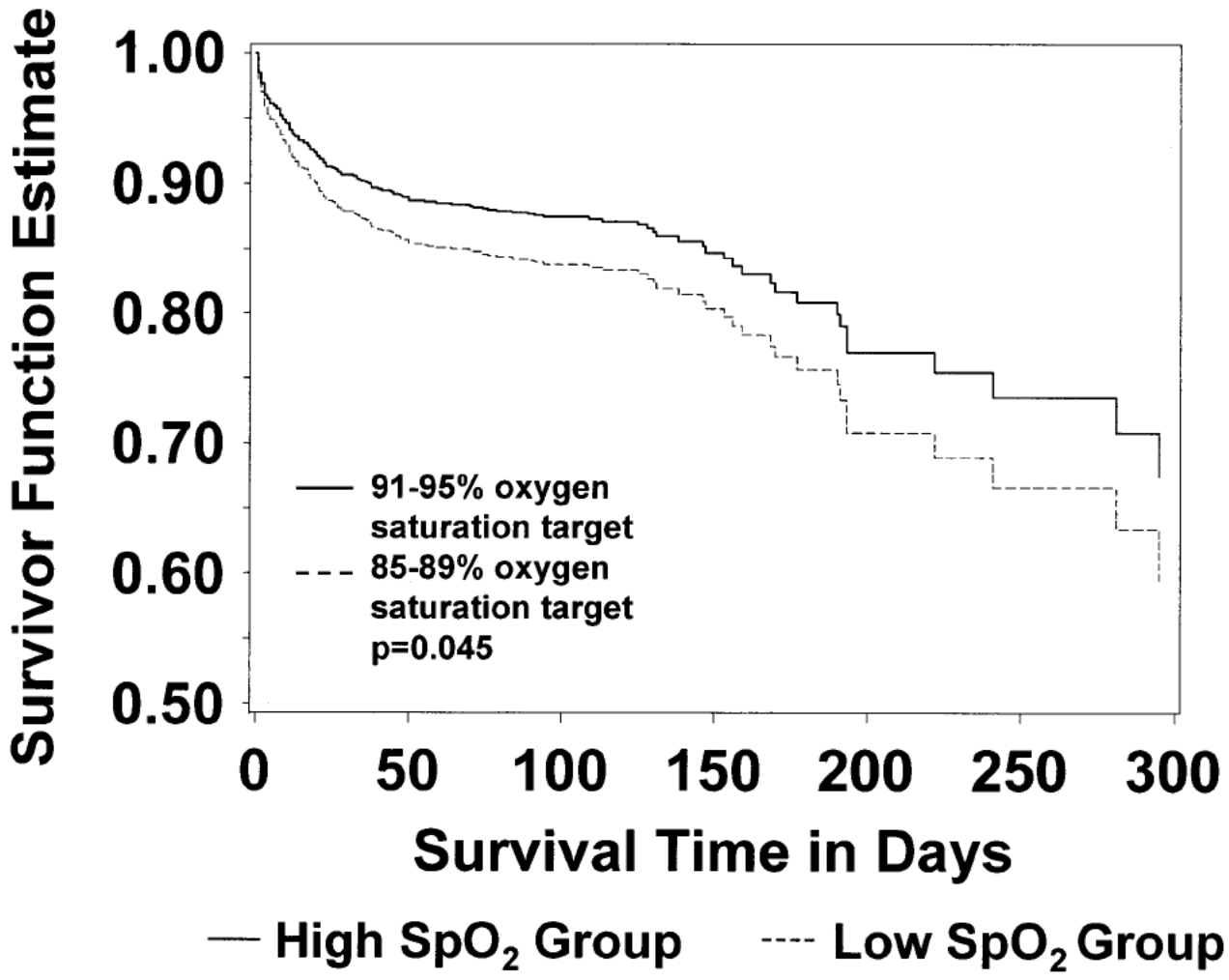

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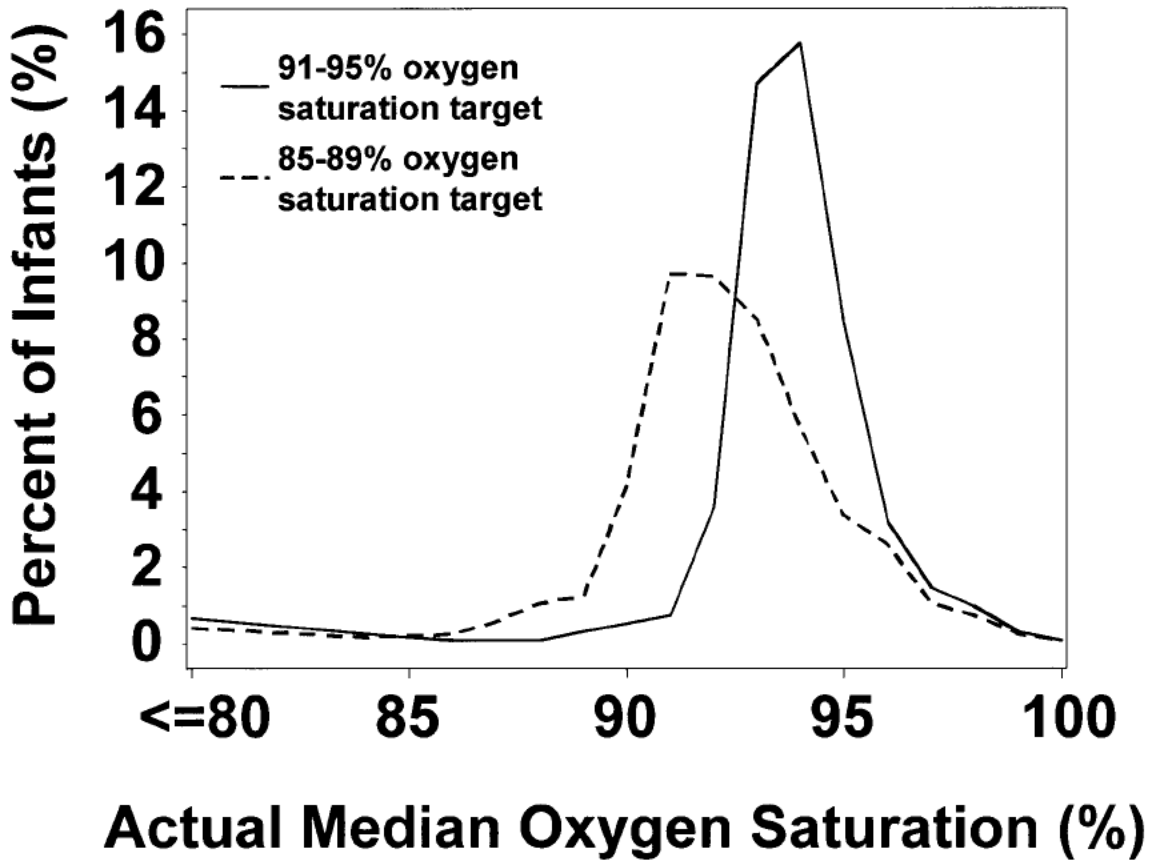
Figure 3.



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The authors have seen and approved the final manuscript and have contributed substantially to the conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Manuscript: 2699

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The

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current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were to be intubated in the delivery room and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the receipt of supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (CI 0.82, 1.01), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in

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preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone, whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce subsequent neurodevelopmental impairment.[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with respiratory distress documenting a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[4,5,6,7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11]. There was a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

The SUPPORT trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported

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separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants would result in an increased survival without BPD at 36 weeks using the physiologic definition compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilation begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower target SpO2 range (85% to 89%) with a higher more conventional target SpO2 range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR. CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. Using a conservative 2% level of significance to account for the co-primary outcome of death or severe ROP in the SpO2 arm of this factorial

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trial resulted in a required sample size of 1310 infants. This sample size was not powered to detect an interaction effect between the 2 factorial arms.

The Physiologic Definition of BPD assigned the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314] Pre-specified secondary outcomes included the evaluation of BPD defined by the receipt of oxygen at 36 weeks.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided p value of less than 0.02 was considered statistically significant for the primary outcome of death or BPD. P values for secondary outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons.

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An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation or epinephrine in the delivery room compared with the surfactant infants. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization.

The post delivery room outcomes are provided in Table 3. The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks

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post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified.

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD among survivors to 36 weeks post menstrual age using either the Physiologic Definition or the receipt of oxygen at 36 weeks (Table 3).

There were no significant differences overall for death in the delivery room, length of stay, or days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.011$). There were no significant differences between the groups for air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who were intubated during their nursery course ($p<0.001$). There was a reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2% vs. 13.2%, $p<0.001$) (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention or bevacizumab treatment for ROP among survivors was not different in the CPAP compared to the surfactant infants (Table 3). While the study was not powered to detect an interaction between the two interventions, we prospectively agreed to evaluate such interactions and none were found.

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Strata Results: 24 – 25 weeks Gestation

CPAP infants in this stratum had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this stratum are reported in Appendix Table A2.

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups in this stratum, 10.8% vs 10.2%. (Appendix Table A3).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. In a pilot trial we found that 100% of infants of 23 weeks gestation required intubation in the delivery room, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported trial of Morley et al[10~~10~~15] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven strategy of limited ventilation with infants

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who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation. [Error! Bookmark not defined.~~Error! Bookmark not defined.~~4,Error! Bookmark not defined.~~Error! Bookmark not defined.~~5,Error! Bookmark not defined.~~Error! Bookmark not defined.~~6] The infants who received surfactant were treated with a ventilation approach that was used by a majority of NRN units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the primary outcomes. Data on survival without neurodevelopmental impairment at 18 to 22 months are currently accruing, and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the receipt of oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a clinically significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week stratum. While we did not postulate such a difference in the individual stratum this increased occurrence of death is cause for concern. The 565 infants in our 24 to 25 week stratum to our knowledge represent the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD or death by 36 weeks post menstrual age in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes

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including death in the immature stratum favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Figure 1 – Consort Diagram

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)
	26-27	57.0% (378/663)	57.1% (373/653)
Randomized to Low SpO2 in 2x2 factorial	24-25 weeks GA	49.8% (142/285)	47.9% (134/280)
	26-27 weeks GA	51.3% (194/378)	49.3% (184/373)
Male		51.6% (342/663)	56.7% (370/653)
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)
	Hispanic	20.8% (138/663)	18.5% (121/653)
	Other/unknown	3.2% (21/663)	4.0% (26/653)
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1
Antenatal steroids (any)		96.8% (642/663)	95.6% (623/652)
Antenatal steroids (full course)		73.6% (486/660)	69.8% (453/649)
Death in the DR		0.2% (1/663)	0.8% (5/653)

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661)	25.6% (167/653)	0.92 (0.76, 1.11)	0.38
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.43
PPV in the DR	65.7% (435/662)	92.9% (606/652)	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR	81.1% (538/663)	22.4% (146/653)	3.66 (3.16, 4.25)	<0.0001
Intubated in DR	34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660)	27.0% (176/652)	1.21 (1.02, 1.43)	0.02
Surfactant in DR	14.1% (93/660)	51.4% (335/652)	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU	67.1% (443/660)	98.9% (646/653)	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.48
Epinephrine in DR	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.02

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	47.8% (317/663)	51.0% (333/653)	0.95 (0.85, 1.05)	0.30
BPD (supplemental oxygen) or death by 36 weeks PMA	48.7% (323/663)	54.1% (353/653)	0.91 (0.83, 1.01)	0.07
BPD (physiologic definition) by 36 weeks PMA	39.2% (223/569)	40.6% (219/539)	0.99 (0.87, 1.14)	0.92
BPD (supplemental oxygen) by 36 weeks PMA	40.2% (229/569)	44.3% (239/539)	0.94 (0.82, 1.06)	0.32
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.96
Death by 36 weeks PMA	14.2% (94/663)	17.5% (114/653)	0.81 (0.63, 1.03)	0.09
Death at any time while hospitalized	16.4% (109/663)	19.6% (128/653)	0.84 (0.67, 1.05)	0.13
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0	-1.3 (-6.3, 3.7)	0.60
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6	-3.1 (-7.1, 0.8)	0.12
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1	-3.0 (-5.6, -0.3)	0.03
Discharge on oxygen	22.2% (122/550)	23.9% (124/519)	0.98 (0.8, 1.2)	0.82
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)	0.01
Any air leak in first 14 days	6.8% (45/663)	7.4% (48/653)	0.89 (0.6, 1.32)	0.56
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.15
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1.00 (0.73, 1.36)	0.99
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.12
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005
Severe ROP among survivors	13.1% (67/511)	13.7% (65/473)	0.94 (0.69, 1.28)	0.71

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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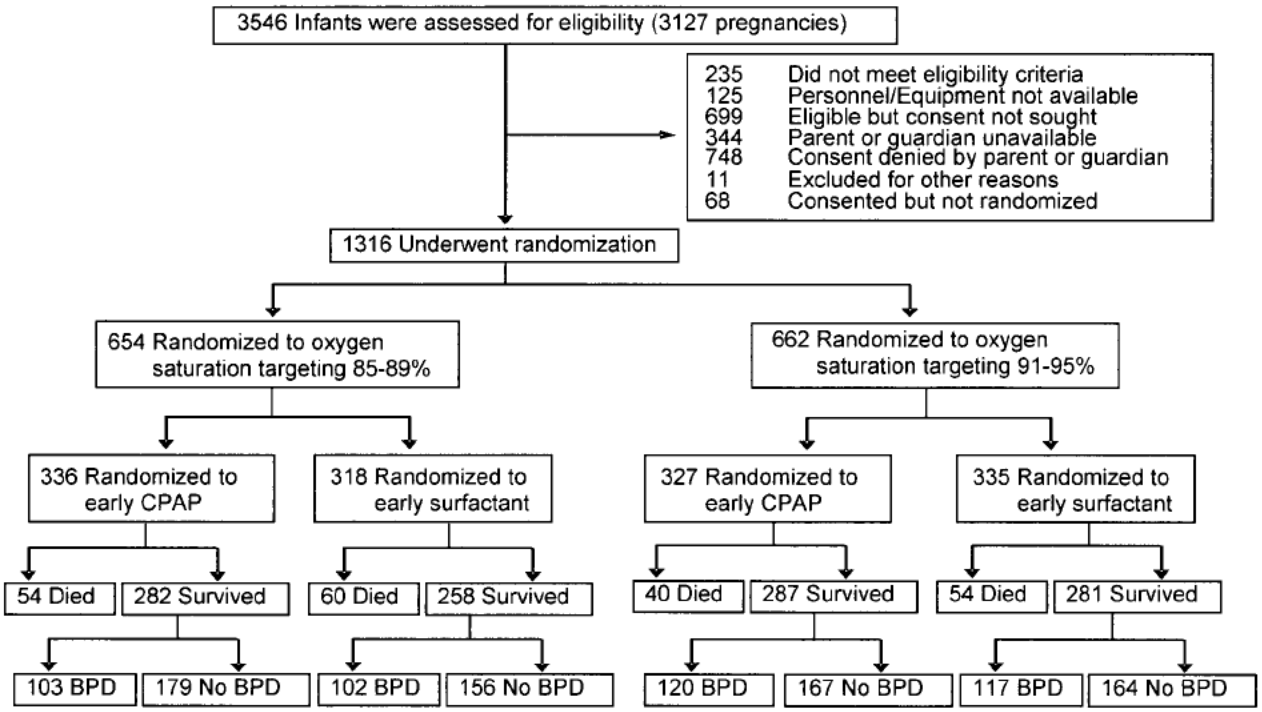
Figure: Consort Diagram

Legend: Flow chart of the screening, random assignment, and primary outcome. Survival is to 36 weeks post menstrual age. BPD denotes bronchopulmonary dysplasia by the physiologic definition. The numbers exclude pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks.



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Appendix Tables

Table A1. Outcomes for 24 to 25 week Stratum

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.45
BPD (supplemental oxygen) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.36
BPD (physiologic definition) by 36 weeks PMA	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.53
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.56
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.01
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.03
Total LOS any hospital* Mean±StdErr (N=405)	122.0 ± 2.9	119.0 ± 3.1	3.0 (-5.1, 11.0)	0.47
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4	0.5 (-5.8, 6.9)	0.86
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6	-3.0 (-7.2, 1.3)	0.17
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.59
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.049
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.40
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.58
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.58
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.39
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.02

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table A2. Cause of Death for 24 to 25 week stratum

Contributory Cause of Death	CPAP (N=68)	Surfactant (N=90)
Respiratory distress syndrome	13/68 (19.1)	31/90 (34.4)
Bronchopulmonary dysplasia	10/68 (14.7)	7/90 (7.8)
Infection	14/68 (20.6)	15/90 (16.7)
Necrotizing enterocolitis	10/68 (14.7)	16/90 (17.8)
Central nervous center insult	11/68 (16.2)	5/90 (5.6)
Immaturity	3/68 (4.4)	5/90 (5.6)
Other	7/68 (10.3)	11/90 (12.2)

Table A3. Outcomes for 26 to 27 week Stratum

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.48
BPD (supplemental oxygen) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.12
BPD (physiologic definition) by 36 weeks PMA	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.08
Death in the first week	4.0% (15/378)	2.7% (10/373)	1.36 (0.61, 3.02)	0.46
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.61
Death at any time while hospitalized	10.8% (41/378)	10.2% (38/373)	1.06 (0.7, 1.6)	0.80
Total LOS any hospital* Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4	-4.0 (-10.4, 2.4)	0.21
Days on supplemental oxygen† Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9	-5.5 (-10.6, -0.4)	0.03
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3	-3.0 (-6.4, 0.4)	0.08
Discharge on oxygen	15.8% (53/336)	19.6% (65/331)	0.88 (0.64, 1.2)	0.41
Alive and off MV (HFV/CV) at 7 days	71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.10
Any air leak in first 14 days	5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.97
Medical or surgical NEC	10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.14
PDA requiring surgery	7.2% (27/374)	6.0% (22/368)	1.22 (0.7, 2.14)	0.49
IVH grade 3-4	10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.17
Postnatal steroids for BPD	2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.008

* Among survivors to discharge, transfer or one year; maximum value is 366 days

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† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Subject: Confidential SUPPORT papers for submission to NEJM

Date: Monday, November 30, 2009 4:42:00 PM

Attachments: Carlo SUPPORT Q2 2009-11-25 CLEAN MASTER.doc
SUPPORT Nov 30 Final.doc
NEJM Tables and Figure Nov 30 Final.doc

Hi

Attached are the two SUPPORT papers for submission to NEJM. They will be submitted later this week.

Thanks to everyone for the **quick work in writing the papers** and the **patience and endurance** to conduct this important trial!!!

Rose

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.21). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy or death but resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3-5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of $\geq$ 92% (3.3 $\pm$ 0.3%) or $\geq$98% (5.6 $\pm$ 1.1%) than in units with lower oxygen saturation targets (1.4 $\pm$ 0.2% and 3.1 $\pm$ 0.3%, respectively).[5] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was

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27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease retinopathy of prematurity, concerns remain about the safety of these oxygen saturation targets.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and two ventilation approaches (continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies). The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent data coordinating center, approved the trial.

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Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). A previous trial used a fixed 3% absolute oxygen saturation offset throughout the entire range of saturations to mask caregivers and separate oxygen saturations in premature infants.[17] The algorithm used in the current trial differed markedly as the oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups. An oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an

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oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display value of 84% corresponded to actual values of 84 and 84-87% in the low and high target groups, respectively. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting compliance. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial's Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New

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Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following occurred: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and

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gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on 36 pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and

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Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.21; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the

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two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was considerable overlap (Figure 3). These data indicate that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome. Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

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This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The increase in mortality in the current trial may be related either to the lower oxygen saturation targets or the use of oxygen restriction started soon after.

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,23] There have not been other randomized controlled trials of different oxygen targeting begun soon after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for

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oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.3)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk† (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value‡
Length of stay any hospital, (days) m+SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m+SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m+SE†	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m+SE†	59.8 ± 1.6	67.4 ± 1.5	0.0002
Continuous positive airway pressure, (days) m+SE†	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27
Present time in actual oxygen saturation range 84-96%, %	66.9 ± 13.9	68.0 ± 13.9	0.16

*Among survivors to discharge, transfer or one year; maximum value is 366 days

†Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes severe retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks. The question marks in the ROP outcome boxes are for infants in whom the first ROP outcome could not be ascertained because of loss to follow up.

Figure 2. Survivor curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. The medians of the distributions were significantly different based on a Rank Sums test ($p < 0.001$).

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Figure 1.

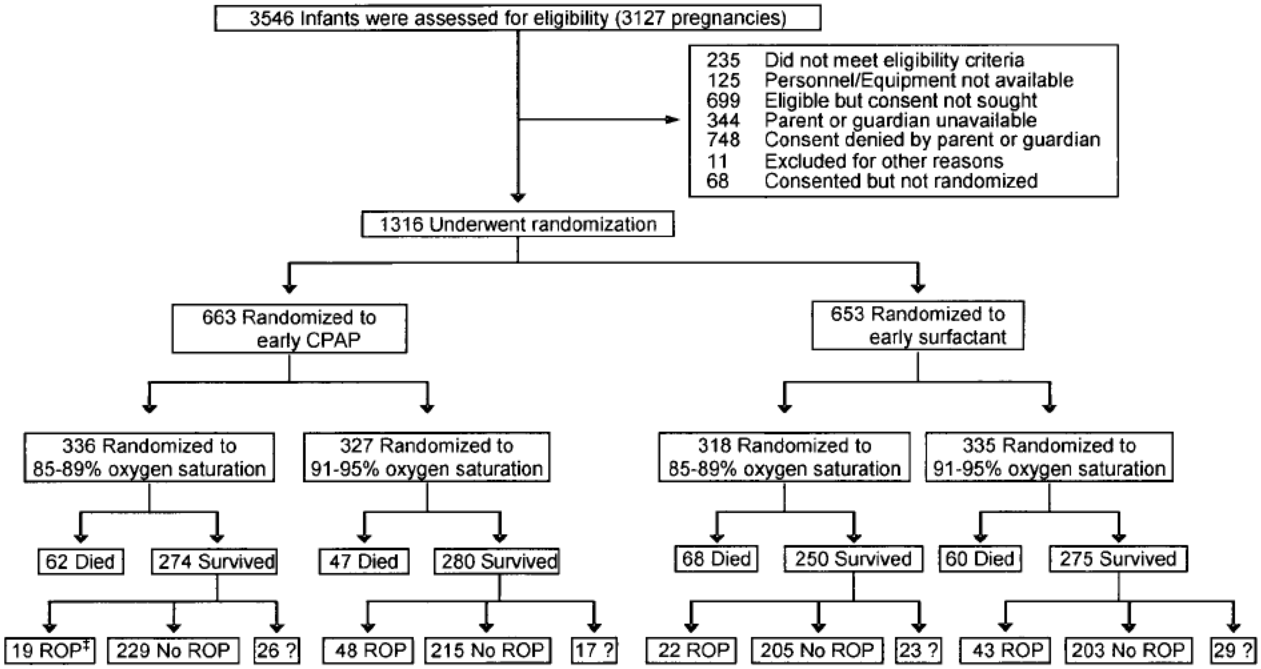

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Figure 2. Survivor Curve for Mortality

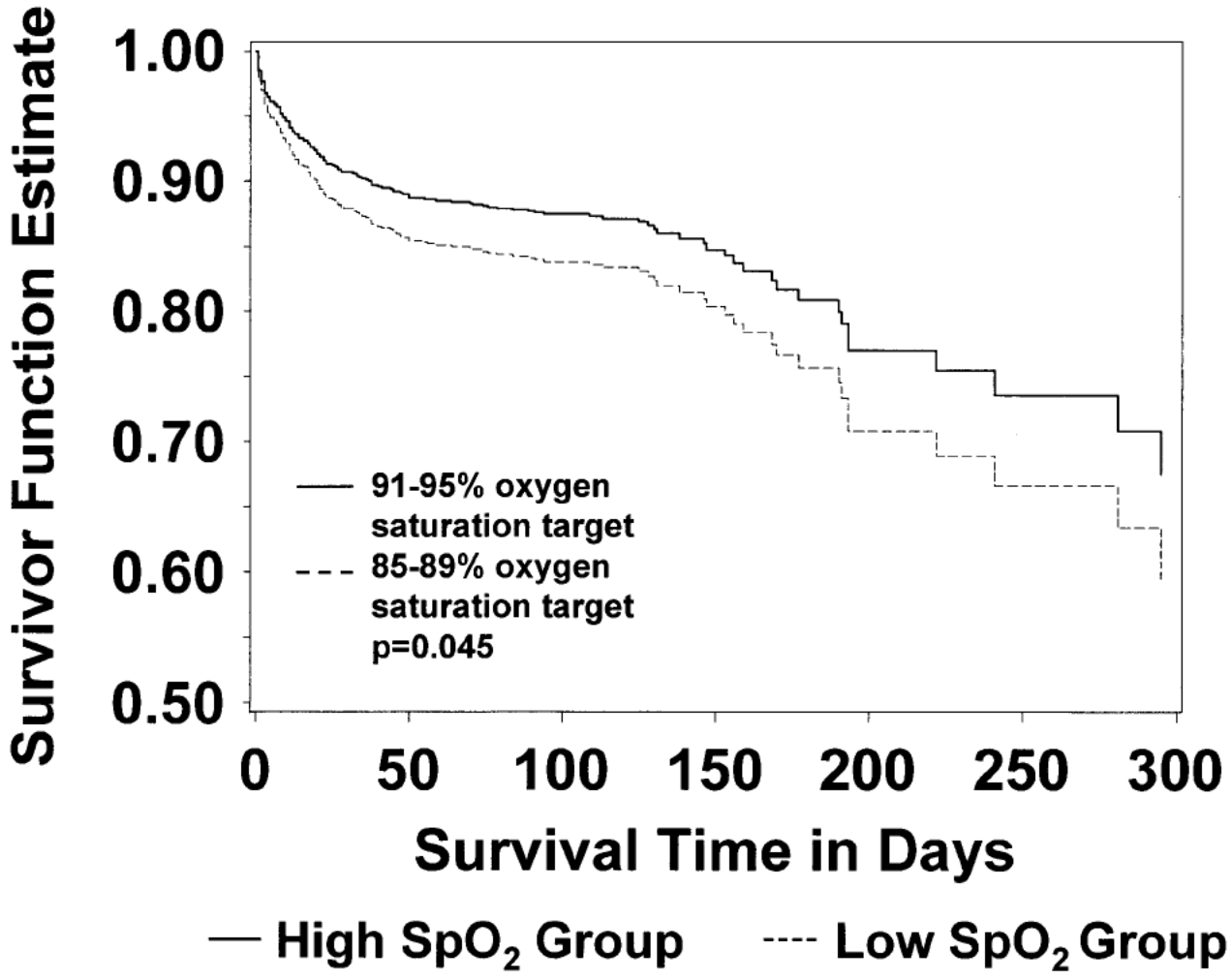

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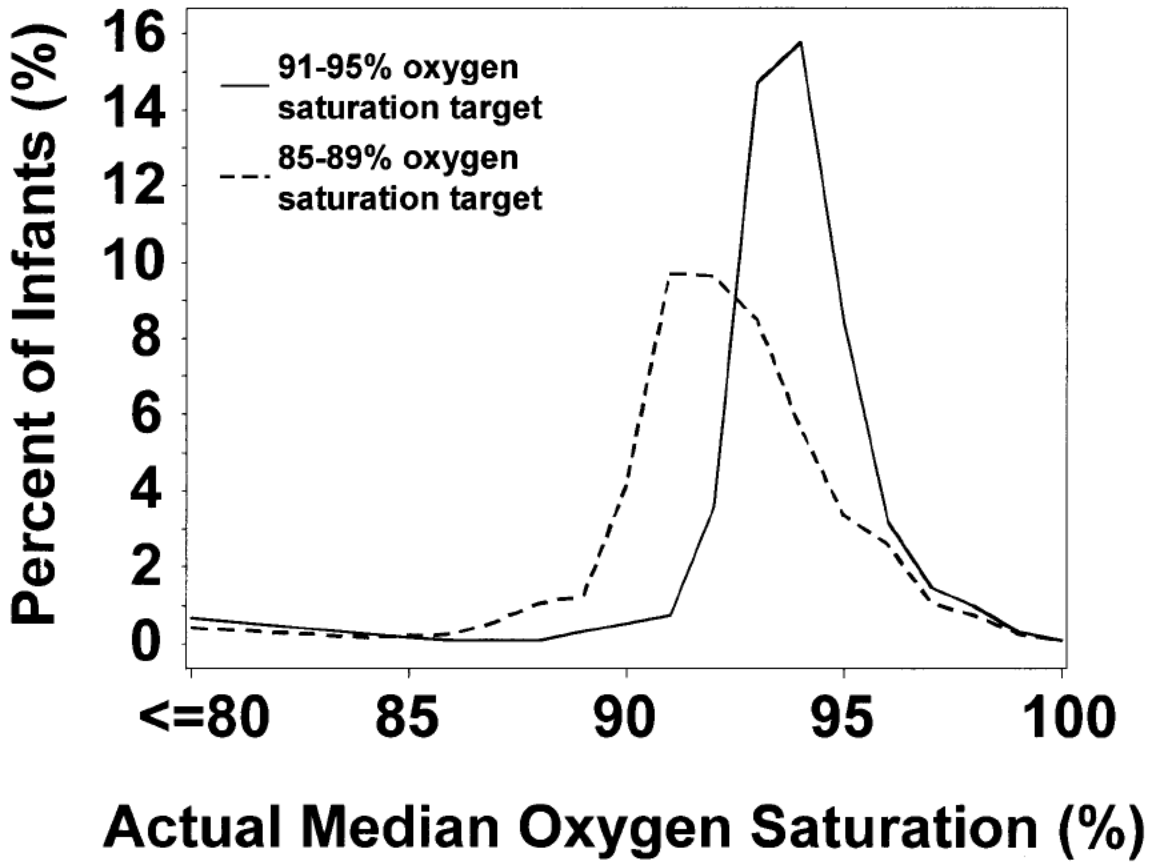
Figure 3.



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to the conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The

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current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were to be intubated in the delivery room and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the receipt of supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (CI 0.82, 1.01), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in

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preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone, whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce subsequent neurodevelopmental impairment. [3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with respiratory distress documenting a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP. [4,5,6,7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11]. There was a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

The SUPPORT trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported

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separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants would result in an increased survival without BPD at 36 weeks using the physiologic definition compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilation begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower target SpO2 range (85% to 89%) with a higher more conventional target SpO2 range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR. CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. Using a conservative 2% level of significance to account for the co-primary outcome of death or severe ROP in the SpO2 arm of this factorial

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trial resulted in a required sample size of 1310 infants. This sample size was not powered to detect an interaction effect between the 2 factorial arms.

The Physiologic Definition of BPD assigned the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314] Pre-specified secondary outcomes included the evaluation of BPD defined by the receipt of oxygen at 36 weeks.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided p value of less than 0.02 was considered statistically significant for the primary outcome of death or BPD. P values for secondary outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons.

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An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation or epinephrine in the delivery room compared with the surfactant infants. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization.

The post delivery room outcomes are provided in Table 3. The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks

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post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified.

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD among survivors to 36 weeks post menstrual age using either the Physiologic Definition or the receipt of oxygen at 36 weeks (Table 3).

There were no significant differences overall for death in the delivery room, length of stay, or days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.011$). There were no significant differences between the groups for air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who were intubated during their nursery course ($p<0.001$). There was a reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2% vs. 13.2%, $p<0.001$) (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention or bevacizumab treatment for ROP among survivors was not different in the CPAP compared to the surfactant infants (Table 3). While the study was not powered to detect an interaction between the two interventions, we prospectively agreed to evaluate such interactions and none were found.

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Strata Results: 24 – 25 weeks Gestation

CPAP infants in this stratum had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this stratum are reported in Appendix Table A2.

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups in this stratum, 10.8% vs 10.2%. (Appendix Table A3).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. In a pilot trial we found that 100% of infants of 23 weeks gestation required intubation in the delivery room, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported trial of Morley et al[10~~10~~15] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven strategy of limited ventilation with infants

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who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation. Error! Bookmark not defined.~~Error! Bookmark not defined.~~4,Error! Bookmark not defined.~~Error! Bookmark not defined.~~5,Error! Bookmark not defined.~~Error! Bookmark not defined.~~6 The infants who received surfactant were treated with a ventilation approach that was used by a majority of NRN units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the primary outcomes. Data on survival without neurodevelopmental impairment at 18 to 22 months are currently accruing, and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the receipt of oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a clinically significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week stratum. While we did not postulate such a difference in the individual stratum this increased occurrence of death is cause for concern. The 565 infants in our 24 to 25 week stratum to our knowledge represent the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD or death by 36 weeks post menstrual age in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes

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including death in the immature stratum favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Figure 1 – Consort Diagram

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)
	26-27	57.0% (378/663)	57.1% (373/653)
Randomized to Low SpO2 in 2x2 factorial	24-25 weeks GA	49.8% (142/285)	47.9% (134/280)
	26-27 weeks GA	51.3% (194/378)	49.3% (184/373)
Male		51.6% (342/663)	56.7% (370/653)
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)
	Hispanic	20.8% (138/663)	18.5% (121/653)
	Other/unknown	3.2% (21/663)	4.0% (26/653)
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1
Antenatal steroids (any)		96.8% (642/663)	95.6% (623/652)
Antenatal steroids (full course)		73.6% (486/660)	69.8% (453/649)
Death in the DR		0.2% (1/663)	0.8% (5/653)

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661)	25.6% (167/653)	0.92 (0.76, 1.11)	0.38
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.43
PPV in the DR	65.7% (435/662)	92.9% (606/652)	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR	81.1% (538/663)	22.4% (146/653)	3.66 (3.16, 4.25)	<0.0001
Intubated in DR	34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660)	27.0% (176/652)	1.21 (1.02, 1.43)	0.02
Surfactant in DR	14.1% (93/660)	51.4% (335/652)	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU	67.1% (443/660)	98.9% (646/653)	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.48
Epinephrine in DR	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.02

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	47.8% (317/663)	51.0% (333/653)	0.95 (0.85, 1.05)	0.30
BPD (supplemental oxygen) or death by 36 weeks PMA	48.7% (323/663)	54.1% (353/653)	0.91 (0.83, 1.01)	0.07
BPD (physiologic definition) by 36 weeks PMA	39.2% (223/569)	40.6% (219/539)	0.99 (0.87, 1.14)	0.92
BPD (supplemental oxygen) by 36 weeks PMA	40.2% (229/569)	44.3% (239/539)	0.94 (0.82, 1.06)	0.32
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.96
Death by 36 weeks PMA	14.2% (94/663)	17.5% (114/653)	0.81 (0.63, 1.03)	0.09
Death at any time while hospitalized	16.4% (109/663)	19.6% (128/653)	0.84 (0.67, 1.05)	0.13
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0	-1.3 (-6.3, 3.7)	0.60
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6	-3.1 (-7.1, 0.8)	0.12
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1	-3.0 (-5.6, -0.3)	0.03
Discharge on oxygen	22.2% (122/550)	23.9% (124/519)	0.98 (0.8, 1.2)	0.82
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)	0.01
Any air leak in first 14 days	6.8% (45/663)	7.4% (48/653)	0.89 (0.6, 1.32)	0.56
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.15
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1.00 (0.73, 1.36)	0.99
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.12
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005
Severe ROP among survivors	13.1% (67/511)	13.7% (65/473)	0.94 (0.69, 1.28)	0.71

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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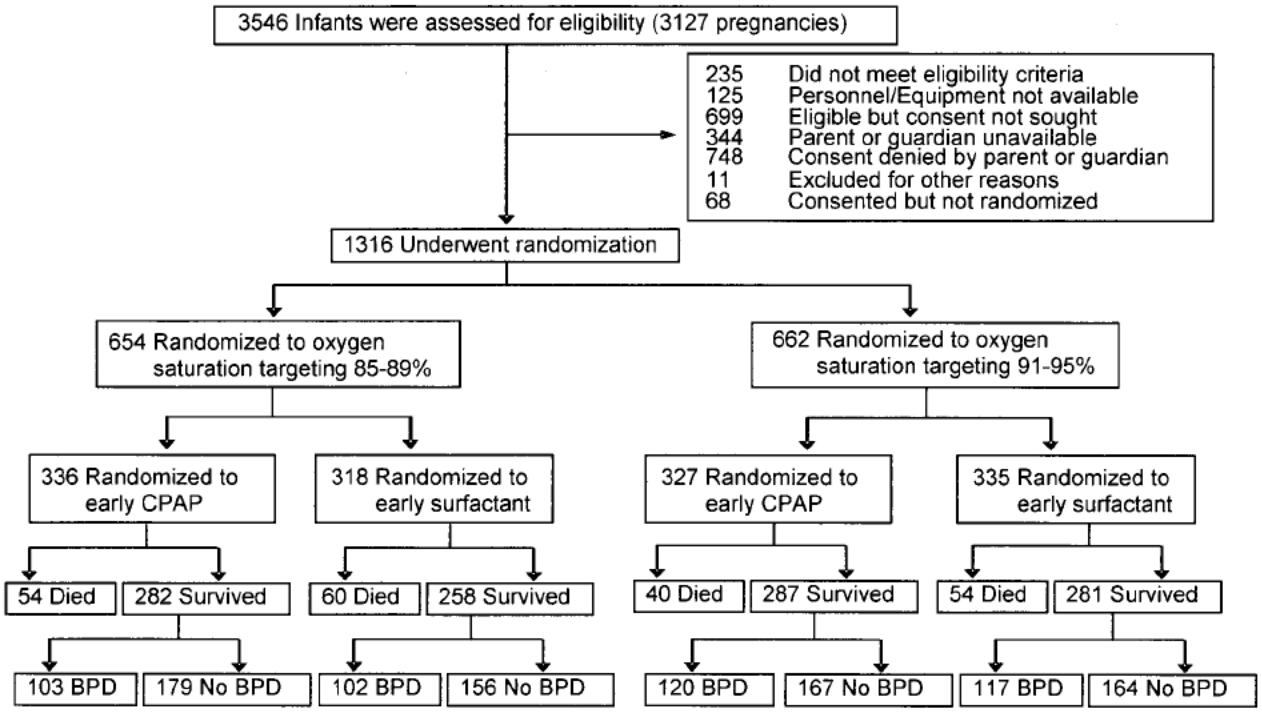
Figure: Consort Diagram

Legend: Flow chart of the screening, random assignment, and primary outcome. Survival is to 36 weeks post menstrual age. BPD denotes bronchopulmonary dysplasia by the physiologic definition. The numbers exclude pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks.



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Appendix Tables

Table A1. Outcomes for 24 to 25 week Stratum

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.45
BPD (supplemental oxygen) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.36
BPD (physiologic definition) by 36 weeks PMA	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.53
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.56
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.01
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.03
Total LOS any hospital* Mean±StdErr (N=405)	122.0 ± 2.9	119.0 ± 3.1	3.0 (-5.1, 11.0)	0.47
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4	0.5 (-5.8, 6.9)	0.86
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6	-3.0 (-7.2, 1.3)	0.17
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.59
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.049
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.40
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.58
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.58
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.39
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.02

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table A2. Cause of Death for 24 to 25 week stratum

Contributory Cause of Death	CPAP (N=68)	Surfactant (N=90)
Respiratory distress syndrome	13/68 (19.1)	31/90 (34.4)
Bronchopulmonary dysplasia	10/68 (14.7)	7/90 (7.8)
Infection	14/68 (20.6)	15/90 (16.7)
Necrotizing enterocolitis	10/68 (14.7)	16/90 (17.8)
Central nervous center insult	11/68 (16.2)	5/90 (5.6)
Immaturity	3/68 (4.4)	5/90 (5.6)
Other	7/68 (10.3)	11/90 (12.2)

Table A3. Outcomes for 26 to 27 week Stratum

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.48
BPD (supplemental oxygen) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.12
BPD (physiologic definition) by 36 weeks PMA	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.08
Death in the first week	4.0% (15/378)	2.7% (10/373)	1.36 (0.61, 3.02)	0.46
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.61
Death at any time while hospitalized	10.8% (41/378)	10.2% (38/373)	1.06 (0.7, 1.6)	0.80
Total LOS any hospital* Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4	-4.0 (-10.4, 2.4)	0.21
Days on supplemental oxygen† Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9	-5.5 (-10.6, -0.4)	0.03
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3	-3.0 (-6.4, 0.4)	0.08
Discharge on oxygen	15.8% (53/336)	19.6% (65/331)	0.88 (0.64, 1.2)	0.41
Alive and off MV (HFV/CV) at 7 days	71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.10
Any air leak in first 14 days	5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.97
Medical or surgical NEC	10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.14
PDA requiring surgery	7.2% (27/374)	6.0% (22/368)	1.22 (0.7, 2.14)	0.49
IVH grade 3-4	10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.17
Postnatal steroids for BPD	2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.008

* Among survivors to discharge, transfer or one year; maximum value is 366 days

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† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Monday, November 30, 2009 2:31:00 PM

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Monday, November 30, 2009 2:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: VOTE:SUPPORT

Yes on both
BJS"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee.
1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.

X yes no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.

X yes no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.

X yes no
I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Monday, November 30, 2009 1:47 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; Wally Carlo; Abhik Das
Subject: Re: CPAP final
Attachments: SUPPORT Nov 30 Final.doc; NEJM Tables and Figure Nov 30 Final.doc

Hi Rose
Marie made a few final edits, and I have reviewed. This is the final. Please check or modify the boilerplate as needed.
I hope that both manuscripts are ready for uploading.
Thanks for all your help
Neil

On 11/25/09 5:50 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

Neil,

I corrected a few typos in this version of the paper (mostly I deleted extra spaces). I'm not sure I got all typos, though, so someone else might want to take a look. On page 16 in the Results you say "ROP among" which should either be "ROP among survivors" (which would be most accurate) or else "among" should be deleted. I also commented that the p values in the text sometimes use more digits than those in the tables (ex. 0.011 vs. 0.01) and I wonder if they need to be consistent. In the attached version of the tables I deleted where I had the source forms in parentheses, ex. "(SUPP03)" but there are still lots of abbreviations (DR, PPV, PDA, etc) that I wonder if we need to write out.

It's exciting to have this just about done!

FYI, I will be unavailable for a couple of hours this morning, but I will be back by noon if you need anything. I plan to take off on my 8 hour drive to Virginia before the Neoprom call but I will call in from the car (on mute to the extent possible).

Happy Thanksgiving, everyone!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 24, 2009 9:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie
Subject:

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Hello Rose
Here is the Final paper and Tables and figures. There were a few remaining errors that I have corrected.
Please let me know when we can upload.
Thanks
Neil

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Monday, November 30, 2009 12:50 PM
To: Gantz, Marie; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Cc: Marsha (UAB)
Subject: Re: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Thanks Marie
Is the CPAP- Surf paper now finalized??
Neil

On 11/30/09 9:32 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

Hi Wally,

I have a few comments:

1) On page 12, instead of "Research Triangle International" RTI should be referred to as "RTI International."
2) On page 17, you removed the number of secondary outcomes analyzed for the population as a whole but left the number of secondary outcomes tested within the GA strata. I didn't know if you intended to delete one number and not the other.
3) You added "Present time in actual oxygen saturation range 84-96%, %" to Table 2, however, there are the following problems:
a. Instead of "Present time" I think the variable label should read "Percent of time" and it should be noted that only time on supplemental oxygen is included.
b. The numbers presented are mean +/- SD.
c. The values in the high SpO2 group should be 68.0 +/- 15.2
d. We decided to do an unadjusted test, thus the p value is unadjusted, not adjusted as noted the column label. Perhaps this information could be presented somewhere other than in Table 2?
4) Figure 1 legend states that "question marks in the ROP outcome boxes are for infants in whom the first ROP outcome could not be ascertained..." Did you mean to say "first ROP outcome" or "final ROP outcome?" I don't know what "first ROP outcome" means.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 25, 2009 3:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.; Marsha Sumner
Subject: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Rose, Neil, Abhik, and Marie:

I am enclosing a revised version which includes suggestions sent to me after the last draft was sent out. There are no substantial changes. I am including tracked changes and a clean copy.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: VOTE:SUPPORT
Date: Sunday, November 29, 2009 10:42:34 AM

From: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sun Nov 29 10:09:44 2009
Subject: RE: VOTE:SUPPORT

See below

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
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713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 8:44 AM
To: Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; Barbara Stoll; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; 'Krisa Van Meurs'; Kennedy, Kathleen A; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Bell, Edward
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
   _x__ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
   _x__yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
   _x__yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: VOTE:SUPPORT
Date: Saturday, November 28, 2009 7:47:19 AM

From: Ronald N Goldberg <goldb008@mc.duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Nov 28 07:02:23 2009
Subject: Re: VOTE:SUPPORT

Hi Rose,
I vote yes for all three requests.
Ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 2739
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

11/24/2009 09:54 AM

To "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "sshankar@med.wayne.edu" <sshankar@med.wayne.edu>, Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "'Krisa Van Meurs'" <vanmeurs@stanford.edu>, "Kathleen.A.Kennedy@uth.tmc.edu" <Kathleen.A.Kennedy@uth.tmc.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "ifrantz@tuftsmedicalcenter.org" <ifrantz@tuftsmedicalcenter.org>, "Bell, Edward" <edward-bell@uiowa.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Das, Abhik" <adas@rti.org>

Subject VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.

___ yes ___no

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___yes ____no

3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.

___yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.

Please respond by November 25

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Friday, November 27, 2009 7:46:34 AM

Confiential

(b) (5) [redacted]

(b) (5) [redacted]

The PAS abstrcats have been submitted and I will get them to you

Have a safe trip

Rose

From: Raju, Tonse (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Sent: Fri Nov 27 02:46:32 2009
Subject: Re: SUPPORT

Thank you. What did the data say?

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Sent: Thu Nov 26 12:59:17 2009
Subject: Re: SUPPORT

The final drafts of the papers are about to be sent through clearance. We are submitting to NEJM. Two abstracts were submitted to PAS and I will get them to you when you return. I will keep you posted

Rose

From: Raju, Tonse (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Sent: Thu Nov 26 10:09:50 2009
Subject: SUPPORT

Hi Rose and Cathy: when will the support paper come out and where? what is the MAIN conclusion. Thanks

Tonse N. K. Raju, MD
Medical Officer
Pregnancy and Perinatology Branch, CDBPM
Eunice Kennedy Shriver National Institute of Child Health and
Human Development, NIH,
6100 Executive Blvd, Bethesda, 20892
Phone: 301-402-1872

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From:	Wally Carlo, M.D.
To:	Higgins, Rosemary (NIH/NICHD) [E]; Ed Donovan (E-mail); Michele Walsh (E-mail); Neil Finer (E-mail); Shahnaz Duara (E-mail); poo@rti.org; wrich@ucsd.edu; Reverett@med.miami.edu
Subject:	RE: SUPPORT
Date:	Saturday, November 27, 2004 10:31:09 AM

Rose: I agree. I think that as part of the oximetry compliance, there should be an analysis of the stored oximetry data to verify the use of alarms and the staff responsiveness to them. wally

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 26, 2004 2:03 PM
To: Ed Donovan (E-mail); Michele Walsh (E-mail); Neil Finer (E-mail); Shahnaz Duara (E-mail); Wally Carlo, M.D.; 'poo@rti.org'; 'wrich@ucsd.edu'; 'Reverett@med.miami.edu'
Subject: SUPPORT

Hi,
I have attached a working draft of items for site compliance for the SUPPORT Trial. Once the Trial is up and running, RTI can assist us with on-site monitoring for compliance to insure adherence to the protocol. A medical person is needed along with the data center for compliance tracking visits. Please comment on the substance of the items to be looked at and feel free to contribute to the document.
Thanks
Happy Black Friday for all of the shoppers!
Rose

Rosemary D. Higgins, M.D.
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Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.786 / Virus Database: 532 - Release Date: 10/29/2004

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From: Archer, Stephanie (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; "wcarlo@peds.uab.edu"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Support authors
Date: Thursday, November 26, 2009 6:48:25 AM
Attachments: Boilerplate, Carlo, SUPPORT Oximetry, 2009-11-26.doc
Boilerplate, Finer, SUPPORT Ventilation, 2009-11-26.doc

Happy Thanksgiving.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 25, 2009 4:09 PM
To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Support authors

See below for Cincinnati - they will have 2 authors per paper - I will have stephanie fix this on the pages.

Thanks

Rose

----- Original Message -----
From: Kurt Schibler <kurt.schibler@chmcc.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 25 10:44:34 2009
Subject: Re: Support authors

Hi Rose,
For the SUPPORT CPAP Paper: Ed Donovan and Vivek Narendran should be listed as authors.
For the SUPPORT Oximetry paper Vivek Narendran and I should be listed.
Happy Thanksgiving!
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
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E-mail: kurt.schibler@cchmc.org

On 11/25/09 10:13 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Kurt
> Cincinnati can have 2 authors for each support paper. Inadvertently, r have
> been placed on the cpap paper. Let me know who should be on each of the
> papers.
>
> Thanks

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> Rose

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SUPPORT Oximetry (without FU)

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[12] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
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Edward F. Bell, MD[20]
Richard A. Ehrenkranz, MD[21]
Kristi L. Watterberg, MD[22]
Rosemary D. Higgins, MD[23]
for the NICHD Neonatal Research Network

Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Case Western Reserve University Rainbow Babies & Children's Hospital (U10 HD21364, GCRC M01 RR80) - Avroy A. Fanaroff, MD; Bonnie S. Siner, RN.

[18] Department of Pediatrics, Wayne State University, Detroit, MI
[19] Wake Forest University School of Medicine, Winston-Salem, NC
[20] Department of Pediatrics, University of Iowa, Iowa City, IA
[21] Department of Pediatrics, Yale University School of Medicine, New Haven, CT
[22] University of New Mexico Health Sciences Center, Albuquerque, NM
[23] Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, GCRC M01 RR30) - Ronald N. Goldberg, MD; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, CTSA UL1 RR25008, GCRC M01 RR39) - Barbara J. Stoll, MD; Susie Buchter, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development - Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, GCRC M01 RR750) - James A. Lemons, MD; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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Stanford University Lucile Packard Children's Hospital (U10 HD27880, CTSA UL1 RR25744, GCRC M01 RR70) - David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (U10 HD53119, GCRC M01 RR54) - John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

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University of California - San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) - Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

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University of Iowa Children's Hospital (U10 HD53109, CTSA UL1 RR24979, GCRC M01 RR59) - John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (U10 HD21397, GCRC M01 RR16587) - Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (U10 HD53089, GCRC M01 RR997) - Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN.

University of Rochester Medical Center Golisano Children's Hospital (U10 HD40521, GCRC M01 RR44) - Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, GCRC M01 RR633) - Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, GCRC M01 RR64) - Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (U10 HD40498, GCRC M01 RR7122) - Nancy J. Peters, RN CCRP.

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Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (U10 HD27871, CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022) - Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Data and Safety Monitoring Committee - Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North

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Anthony J. Piazza, MD	anthony_piazza@oz.ped.emory.edu	No conflicts to report
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T. Michael O'Shea, MD, MPH	moshea@wfubmc.edu	No conflicts to report
Edward F. Bell, MD	edward-bell@uiowa.edu	No conflicts to report
Richard A. Ehrenkranz, MD	richard.ehrenkranz@yale.edu	No conflicts to report

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Rosemary D. Higgins, MD	higginsr@mail.nih.gov	No conflicts to report

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SUPPORT Ventilation (without FU)

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Acknowledgements

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From: Archer, Stephanie (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Publications | Finer, SUPPORT Ventilation
Date: Tuesday, November 24, 2009 3:44:37 PM
Attachments: Finer, SUPPORT Ventilation, 2009-11-24 swa.doc

Here it is.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 24, 2009 2:01 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT NEJM Nov 23 (2)

Can you add NHLBI and DSMC to this one and check the authors?

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

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RTI International (U10 HD36790) – Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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Stanford University Lucile Packard Children's Hospital (U10 HD27880, CTSA UL1 RR25744, GCRC M01 RR70) – David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

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University of Iowa Children's Hospital (U10 HD53109, CTSA UL1 RR24979, GCRC M01 RR59) – John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

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Word count:

Abstract: 244

Manuscript: 2699

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

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Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were to be intubated in the delivery room and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the need for supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (CI 0.82, 1.01), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone, whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce

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subsequent neurodevelopmental impairment.[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with respiratory distress documenting a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[4,5,6,7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11]. There was a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

The SUPPORT trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants would result in an increased survival without BPD at 36 weeks using the

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physiologic definition compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilation begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower target SpO2 range (85% to 89%) with a higher more conventional target SpO2 range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP

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infants were not to be intubated exclusively for surfactant administration in the DR. CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq$88%, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and

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hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. Using a conservative 2% level of significance to account for the co-primary outcome of death or severe ROP in the SpO2 arm of this factorial trial, this resulted in a required sample size of 1310 infants. This sample size was not powered to detect an interaction effect between the 2 factorial arms.

The Physiologic Definition of BPD assigned the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required

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demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314] Pre-specified secondary outcomes included the evaluation of BPD by the receipt of oxygen at 36 weeks.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided p value of less than 0.02 was considered statistically significant for the primary outcome of death or BPD. P values for secondary outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation or epinephrine in the delivery room compared with the surfactant infants. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization.

The post delivery room outcomes are provided in Table 3. The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified.

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD among survivors to 36 weeks post

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menstrual age using either the Physiologic Definition or the receipt of oxygen at 36 weeks (Table 3).

There were no significant differences overall for death in the delivery room, length of stay, or days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups for air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who were intubated during their nursery course (p<0.001). There was a reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2% vs. 13.2%, p<0.001) (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention or bevacizumab treatment for ROP among was not different in the CPAP compared to the surfactant infants (Table 3). While the study was not powered to detect an interaction between the two interventions, we prospectively agreed to evaluate such interactions and none were found.

Strata Results: 24 – 25 weeks Gestation

CPAP infants in this strata had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this strata are reported in Appendix Table A2.

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26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups in this strata, 10.8% vs 10.2%. (Appendix Table A3).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. In a pilot trial we found that 100% of infants of 23 weeks gestation required intubation in the delivery room, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported trial of Morley et al [10~~10~~15] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven strategy of limited ventilation with infants who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation. Error! Bookmark not defined.~~Error!~~

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~~Bookmark not defined.~~4,Error! Bookmark not defined.~~Error! Bookmark not defined.~~5,Error! Bookmark not defined.~~Error! Bookmark not defined.~~6 The infants who received surfactant were treated with a ventilation approach that was used by a majority of NRN units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the primary outcomes. Data on survival without neurodevelopmental impairment at 18 to 22 months are currently accruing, and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the need for oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a clinically significant 8.2% reduction in death in

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the CPAP infants of our 24 to 25 week stratum. While we did not postulate such a difference in the individual stratum this increased occurrence of death is cause for concern. The 565 infants in our 24 to 25 week stratum to our knowledge represent the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD or death by 36 weeks post menstrual age in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes including death in the immature stratum favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Figure 1 – Consort Diagram

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, November 25, 2009 4:08 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org
Cc: Marsha Sumner
Subject: RE: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Wally
There is a problem with following sentence – I think you meant to say after birth – at present in both versions it ends as shown

"in the current trial may be related either to the lower oxygen saturation targets or the use of oxygen restriction

started soon after. "

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 25, 2009 12:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org
Cc: Wally Carlo, M.D.; Marsha Sumner
Subject: The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Rose, Neil, Abhik, and Marie:

I am enclosing a revised version which includes suggestions sent to me after the last draft was sent out. There are no substantial changes. I am including tracked changes and a clean copy.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, November 25, 2009 10:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Finer SUPPORT Ventilation 2009-11-24 swa

Thanks Rose
Happy Thanksgiving to you and your family!!!
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 25, 2009 7:21 AM
To: Finer, Neil
Subject: Re: Finer SUPPORT Ventilation 2009-11-24 swa

Neil
Sorry for the delay- I have asked Kurt to designated 2 authors (not 3) for both papers. Ed and kurt served on the subcommittee. Vivek was the site PI. For other sites with a subcommittee member and a separate site PI, we noramlly allow a second, but not a third, author. I will also check wally's paper.

Thanks for pointing this out (sorry for the delay - I had computer problems which are now resolved).

Happy thanksgiving! And enjoy the grandkids!
Rose

From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Tue Nov 24 21:37:01 2009
Subject: RE: Finer SUPPORT Ventilation 2009-11-24 swa

Hi Rose
I would still like to know why we have 3 authors from Cincinnati?
Ed Donovan appears as an author and in the Boilerplate – this is interesting as other site NRN PIs such as Richard are not authors but appear in the boilerplate. To my knowledge Vivek was not on the subcommittee.
Please let me know why this is- I have agreed to the authorship methodology – but I do not agree with singling out this center, What am I missing?
Is this the same for Wally's paper?
I have not asked for much from the NRN – I would now respectfully request an answer.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 12:46 PM
To: Finer, Neil
Subject: Finer SUPPORT Ventilation 2009-11-24 swa

Neil
Stephanie has added the changes to the authorship and boilerplate - can you forward me the "Final" copy for NICHD clearance?

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Thanks
Rose

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, November 25, 2009 10:24 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; Rich, Wade; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; edward.donovan@cchmc.org; Nancy Newman; IFrantz@tufts-nemc.org; susie.buchter@oz.ped.emory.edu; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Laroia, Nirupama; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; Vivek.Narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Oxygen Saturation Manuscript - Final?
Attachments: O2 Saturation 11 24 09 CLEAN MASTER NR rev.doc

Hi Wally
I found a few typos and 2 suggestions. I would not refer to Askie algorithm as it was so different from ours - it never returns to a normal value and was not tapered etc.
Great job - I leave the final decisions to you Thanks for being such a wonderful partner for me.
Be well and all the best for Thanksgiving Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 10:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; mcw3@cwru.edu; Rich, Wade; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; edward.donovan@cchmc.org; Nancy Newman; IFrantz@tufts-nemc.org; susie.buchter@oz.ped.emory.edu; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Laroia, Nirupama; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; Vivek.Narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Oxygen Saturation Manuscript - Final?

Dear All:

Thanks to everyone for their comments. I have incorporated as many of your comments as possible.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: VOTE:SUPPORT
Date: Wednesday, November 25, 2009 10:16:11 AM

----- Original Message -----
From: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 25 03:13:58 2009
Subject: Re: VOTE:SUPPORT

yes, to all--happy thanksgiving, rose--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/24/09 8:43 AM >>>
For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:
1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
_xx__ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
_xx__yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
_xx__yes ____ no
I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, November 24, 2009 9:53 PM
To: Gantz, Marie; Abhik Das
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Thanks Marie!!
This should do it - but you never know.
Be well and have a wonderful Thanksgiving Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, November 24, 2009 1:18 PM
To: Finer, Neil; Abhik Das
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Neil,

Your tables are attached. I added differences in means for the continuous variables, and I rounded the p-values as Wally had done in his paper. I replaced ROP/death in table 3 with ROP among survivors, and I removed ROP/death from the GA strata tables for consistency. I also added a legend to figure 1 to correspond to what Wally had for his CONSORT figure.

Let me know if you need anything else.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 23, 2009 2:16 PM
To: Gantz, Marie; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: ++++CONFIDENTIAL: CPAP vs SURF

THANKS Marie
Can I leave you to modify the Tables accordingly??
Neil

On 11/23/09 10:48 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

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> I agree on the p-value issues. Abhik has also suggested adding
adjusted
> differences and CIs for the continuous outcomes in the tables to
> correspond to the RRs and CIs for the categorical outcomes. I will add
> those. I am also doing the same for Wally's paper.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Monday, November 23, 2009 10:29 AM
> To: Das, Abhik
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
> Subject: Re: ++++CONFIDENTIAL: CPAP vs SURF
>
> OK Lets leave it
> Thanks
> Neil
>
>
> On 11/23/09 7:25 AM, "Abhik Das" <adas@rti.org> wrote:
>
>> These are not outcomes per se in table 2, so I personally don't see
> why
>> they would be red flags.
>>
>> Thanks
>>
>> Abhik
>>
>> -----Original Message-----
>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>> Sent: Monday, November 23, 2009 10:18 AM
>> To: Das, Abhik
>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
>> Subject: Re: ++++CONFIDENTIAL: CPAP vs SURF
>>
>> HI Abhik
>> I agree - We do have the RR so are the p values additive or a red
flag
>> to a
>> bull - read that as reviewers!!
>> Neil
>>
>>
>> On 11/23/09 6:47 AM, "Abhik Das" <adas@rti.org> wrote:

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>>
>>> I don't think table 1 has any p values currently. As for table 2, I
>>> don't feel strongly about this, but some people may like to see that
>> the
>>> intervention in fact was delivered as intended; and presenting the p
>>> values may help establish that explicitly.
>>>
>>> Thanks
>>>
>>> Abhik
>>>
>>> -----Original Message-----
>>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>>> Sent: Monday, November 23, 2009 9:44 AM
>>> To: Michael O`Shea
>>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
>>> Subject: Re: ++++CONFIDENTIAL: CPAP vs SURF
>>>
>>> Thanks Mike
>>> We will relook at these.
>>> I think that we had nade a similar decision in previous iiterations
>>> and then others wanted the p vales in Marie and Anhik - can we
>>> review?
>>> Thanks
>>>
>>> Sent from my iPhone
>>>
>>> On Nov 23, 2009, at 4:18 AM, "Michael O`Shea" <moshea@wfubmc.edu>
>> wrote:
>>>
>>>> Neil,
>>>>
>>>> Congratulations on completing this trial - an amazing
>>>> accomplishment. In the attached I offer a few editing suggestions.
>>>>
>>>> In Table 1, I would not include p values, as these are pre-
>>>> randomization variables and the interpretation of a non-significant
>>>> p value is that the difference between groups is not larger than
can
>>>> be explained by chance. But since we know that any differences are
>>>> explained by chance (i.e., randomization), why do we need p values.
>>>>
>>>> In Table 2, I would not include p values, as any differences cannot
>>>> be attributed to chance, as they are processes that were prescribed
>>>> by the protocol with the intention of being different.
>>>>
>>>> In Table 3 I would round the p value to one significant digit.
>>>>
>>>> Thanks so much for your efforts.
>>>>
>>>> Mike
>>>>

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>>>> _____
>>>>
>>>> From: Higgins, Rosemary (NIH/NICHD) [E]
>> [mailto:higginsr@mail.nih.gov]
>>>> Sent: Sat 11/14/2009 2:38 AM
>>>> To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu';
>>> 'sshankar@med.wayne.edu
>>>> '; 'bsood@med.wayne.edu'; 'susie.buchter@oz.ped.emory.edu';
>>> 'Anthony.Piazza@oz.ped.emory.edu
>>>> '(b) (6) 'bpoindex@iupui.edu';
>>> 'kurt.schibler@cchmc.org
>>>> '; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu';
>>> 'edward.donovan@cchmc.org
>>>> '; 'richard.ehrenkranz@yale.edu'; 'alaptook@WIHRI.org';
>>> 'vanmeurs@leland.stanford.edu
>>>> '; 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org';
>>> 'Kathleen.A.Kennedy@uth.tmc.edu
>>>> '; 'Jon.E.Tyson@uth.tmc.edu'; Michael O`Shea;
>>>> 'mcaplan@northshore.org'; 'Nirupama_Laroia@URMC.Rochester.edu';
>>> 'dale_phelps@urmc.rochester.edu
>>>> '; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu';
>>> 'mgantz@rti.org
>>>> '; 'ifrantz@tuftsmedicalcenter.org'; 'edward-bell@uiowa.edu';
>>> 'kwatterberg@salud.unm.edu
>>>> '; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu';
>>> 'cotte010@mc.duke.edu
>>>> '; 'goldb008@mc.duke.edu'
>>>> Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org';
>>> 'mcunningham@rti.org
>>>> '; 'petrie@rti.org'
>>>> Subject: ++++CONFIDENTIAL: CPAP vs SURF
>>>>
>>>>
>>>>
>>>> Hi-
>>>> Here is the most recent draft of the CPAP/surfactant paper.
>>>>
>>>> We will discuss on Monday's call.
>>>>
>>>> Thanks for all the assistance
>>>>
>>>>
>>>> Rose
>>>>
>>>> ----- Original Message -----
>>>> From: Finer, Neil <nfiner@ucsd.edu>
>>>> To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary
(NIH/NICHD)
>>>> [E]; Rich, Wade <wrich@ucsd.edu>
>>>> Sent: Thu Nov 12 17:06:37 2009
>>>> Subject: CPAP vs SURF
>>>>

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>>>> Wally and Rose
>>>> Here is the "final" CPAP vs Surf paper It fits NEJM and
>>>> incorporates all suggestions although some were opposite so we made
>>>> some choices.
>>>> Please review
>>>> Wally can you make sure our definitions for BPD etc are identical??
>>>> Thanks
>>>> I would like to get these submitted Please share with me your
>>>> thoughts Be well Neil
>>>>
>>>>
>>>> <SUPPORT NEJM Nov12 Final-oshea edits.doc>
>>
>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "goldb008@mc.duke.edu"
Subject: Re: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 6:45:24 PM

There are 2 folks from Utah on the subcommittee (similar to mike and you on genomics).

The remainder of the items have been brought up by each site.

Rose

From: Ronald N Goldberg <goldb008@mc.duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 24 18:00:06 2009
Subject: Re: VOTE:SUPPORT

Hi Rose,
I'm not sure I understand the reason for these changes. I thought authorship was based on our guidelines. Has it become a vote? And why are there 2 people from Utah for instance? I find this email a little unsettling since I thought this was all set and agreed upon.
Ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 2739
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

11/24/2009 09:54 AM

To "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "sshankar@med.wayne.edu" <sshankar@med.wayne.edu>, Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "'Krisa Van Meurs'" <vanmeurs@stanford.edu>, "Kathleen.A.Kennedy@uth.tmc.edu" <Kathleen.A.Kennedy@uth.tmc.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "ifrantz@tuftsmedicalcenter.org" <ifrantz@tuftsmedicalcenter.org>, "Bell, Edward" <edward-bell@uiowa.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Das, Abhik" <adas@rti.org>

Subject VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have

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been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.

___ yes ___no

2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.

___yes ____no

3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.

___yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.

Please respond by November 25

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"
Subject: Finer SUPPORT Ventilation 2009-11-24 swa
Date: Tuesday, November 24, 2009 3:45:00 PM
Attachments: Finer SUPPORT Ventilation 2009-11-24 swa.doc

Neil
Stephanie has added the changes to the authorship and boilerplate - can you forward me the "Final" copy for NICHD clearance?
Thanks
Rose

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT, CCRC[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; ~~Namasivayam Ambalavanan, MD[2],~~ Kurt Schibler[8]; Edward F. Donovan[8]; ~~Vivek Narendran, MD MRCP[8];~~ Nancy S. Newman, RN[3]; Namasivayam Ambalavanan, MD[2]; Ivan D. Frantz III, MD[9]; Susie Buchter, MD[10]; Pablo J. Sánchez, ~~MD[10]~~MD[11], ~~Susie Buchter, MD[11]; Brenda H. Morris, MD~~Kathleen A. Kennedy, MD, MPH[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P. Van Meurs, MD[16]; ~~Beena Sood. MD, MS[17];~~ Shahnaz Duara, ~~MD[18]~~MD[17]; Vivek Narendran, MD MRCP[8]; Beena G. Sood, MD, MS[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Vineet Bhandari, MD, DM[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta,

Formatted: Not Superscript/ Subscript

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Atlanta, GA; [10][1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]~~Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA;~~ [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]University of Miami Miller School of Medicine, Miami, FL; ~~[17]Department~~ [18]Department of Pediatrics, Wayne State University, Detroit, MI; ~~[18]University of Miami Miller School of Medicine, Miami, FL;~~ [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22] University of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

Neil N Finer, M.D. Phone: (919) 543 3285

University of California at San Diego Fax: (619) 543 3812

402 Dickinson St., MPF 1-140

San Diego, CA 92103-8774 Email: nfiner@ucsd.edu

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

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Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were to be intubated in the delivery room and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the need for supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (CI 0.82, 1.01), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone, whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce

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subsequent neurodevelopmental impairment. [3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with respiratory distress documenting a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP. [4,5,6,7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11]. There was a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

The SUPPORT trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants would result in an increased survival without BPD at 36 weeks using the

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physiologic definition compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilation begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower target SpO2 range (85% to 89%) with a higher more conventional target SpO2 range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP

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infants were not to be intubated exclusively for surfactant administration in the DR. CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and

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hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. Using a conservative 2% level of significance to account for the co-primary outcome of death or severe ROP in the SpO2 arm of this factorial trial, this resulted in a required sample size of 1310 infants. This sample size was not powered to detect an interaction effect between the 2 factorial arms.

The Physiologic Definition of BPD assigned the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required

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demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314] Pre-specified secondary outcomes included the evaluation of BPD by the receipt of oxygen at 36 weeks.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided p value of less than 0.02 was considered statistically significant for the primary outcome of death or BPD. P values for secondary outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation or epinephrine in the delivery room compared with the surfactant infants. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization.

The post delivery room outcomes are provided in Table 3. The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified.

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD among survivors to 36 weeks post

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menstrual age using either the Physiologic Definition or the receipt of oxygen at 36 weeks (Table 3).

There were no significant differences overall for death in the delivery room, length of stay, or days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups for air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who were intubated during their nursery course (p<0.001). There was a reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2% vs. 13.2%, p<0.001) (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention or bevacizumab treatment for ROP among was not different in the CPAP compared to the surfactant infants (Table 3). While the study was not powered to detect an interaction between the two interventions, we prospectively agreed to evaluate such interactions and none were found.

Strata Results: 24 – 25 weeks Gestation

CPAP infants in this strata had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this strata are reported in Appendix Table A2.

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26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups in this strata, 10.8% vs 10.2%. (Appendix Table A3).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. In a pilot trial we found that 100% of infants of 23 weeks gestation required intubation in the delivery room, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported trial of Morley et al[10~~10~~15] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven strategy of limited ventilation with infants who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.~~Error!~~**

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~~Bookmark not defined.~~4,Error! Bookmark not defined.~~Error! Bookmark not defined.~~5,Error! Bookmark not defined.~~Error! Bookmark not defined.~~6 The infants who received surfactant were treated with a ventilation approach that was used by a majority of NRN units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the primary outcomes. Data on survival without neurodevelopmental impairment at 18 to 22 months are currently accruing, and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the need for oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a clinically significant 8.2% reduction in death in

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the CPAP infants of our 24 to 25 week stratum. While we did not postulate such a difference in the individual stratum this increased occurrence of death is cause for concern. The 565 infants in our 24 to 25 week stratum to our knowledge represent the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD or death by 36 weeks post menstrual age in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes including death in the immature stratum favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

---

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Figure 1 – Consort Diagram

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, November 24, 2009 3:17 PM
To: Das, Abhik
Cc: Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: Re: Support information.

All of this makes me more concerned about the use of the physiologic definition Fortunately or not no sig differences found - a worry for another day Neil

Sent from my iPhone

On Nov 24, 2009, at 11:36 AM, "Das, Abhik" <adas@rti.org<mailto:adas@rti.org>> wrote:

Unfortunately, Kris has looked, but so far has not been able to find anything definitive written in the GDB, Phys Def, or Benchmarking documents that would have precluded sites from using the skewed oximeters to determine either oxygen use at 36 weeks (which goes to the traditional definition of BPD), or to determine eligibility for physiologic challenge (which goes to the physiologic definition of BPD). She did talk to Nancy Newman at Case who says the same thing as Monica below, with regards to the actual challenge. Kris continues to look through her emails and such, but I am not sure what else we can do at this point.

Thanks

Abhik

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, November 24, 2009 11:11 AM
To: Finer, Neil; Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: Support information.

Kris is looking into it.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 24, 2009 12:09 PM
To: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

We are looking for a technical memo on this – do any of you know of such a memo??

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Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 8:18 AM
To: Gantz, Marie; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

I agree. But Jon says that their RNs used the altered oximeters to determine the need for the phys test

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, November 24, 2009 10:12 AM
To: Wally Carlo, M.D.; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

How did they know whether the baby had majority saturation >=90% based on the altered oximeters? An actual saturation of 90% would have corresponded to a display value of 87 or 93 depending on whether the low or high oximeter was used.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 11:08 AM
To: Gantz, Marie; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Support information.

This is what I got from Monica but we should try to find if we have some official documentation of this.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street

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525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Monica Collins
Sent: Tuesday, November 24, 2009 9:58 AM
To: Wally Carlo, M.D.
Subject: RE: Support information.

It was decided based on their status at 36 weeks--they were on the Massimos at that time. However, as part of the physiologic reduction, all babies were put on a unit (nonblinded, nonskewed) oximeter for a baseline period, then reduced if continuing to meet the criteria for reduction. There should have been no difference in failure rate in the babies who were in the high sat group vs. the low sat group.
Monica

From: Wally Carlo, M.D.
Sent: Mon 11/23/2009 6:12 PM
To: Monica Collins; Shirley Cosby
Subject: FW: Support information.
Monica and Shirley:

Did we decide on the need for physiologic test based on the study oximeter or the regular one?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Monday, November 23, 2009 6:01 PM
To: Wally Carlo, M.D.
Cc: Kennedy, Kathleen A
Subject: FW: Support information.

Here is the info I got. Is it incorrect?

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030

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voice 713-500-5651
fax 713-500-0519

From: Mcdavid, Georgia E
Sent: Monday, November 23, 2009 1:38 PM
To: Tate, Patti L; Tyson, Jon E
Cc: Kennedy, Kathleen A
Subject: RE: Support information.

Are we all clear about this? The study oximeter was in place on the 36 week date (we removed it the next day). Whether or not an infant is reduced using the Physiologic Definition is determine by the effective oxygen on that 36 week day. We had a week after the 36 week date to perform the physiologic definition.

From: Tate, Patti L
Sent: Friday, November 20, 2009 10:54 AM
To: Tyson, Jon E
Cc: Kennedy, Kathleen A; Mcdavid, Georgia E
Subject: RE: Support information.

Dr. Tyson, I believe that Dr. Kennedy's assessment is correct. All the centers should have done it the same way. The Masimo oximeter stayed on the infant through the 36 week date and BPD criteria is on the 36 week date. The reduction is to be done within 1 week of the 36+1 week date. 1. Oxygen by NC <27% effective oxygen and the majority of saturations greater than or equal to 90% in the prior 24 hours is eligible for reduction. 2. Oxygen by NC 27-30% effective oxygen and the majority of saturations greater than or equal to 96% in the prior 2 hours are eligible for reduction. 3. Room air NC at any liter flow is eligible for reduction. The Masimo oximeters displayed a target of 88-92% on both the high and low range altered oximeters. Low range was actual 85-89% target and the high range was actual 91-95% target. Since the study monitor was removed from the infant on the 36+1 date the reductions were done on the unit monitors and this should be consistent with all the centers. I have the MOP in the office of both the Support and BPD if you need them. I hope that this helps.

From: Tyson, Jon E
Sent: Friday, November 20, 2009 5:41 AM
To: Tate, Patti L; Mcdavid, Georgia E
Subject: RE: Support information.

Can we be really sure that % in room air at 36 wks was not influenced by study monitor? Can you forward me the MOP, tell me what page to look at, and let's discuss by phoen or in person?

From: Tyson, Jon E
Sent: Friday, November 20, 2009 5:05 AM
To: Tate, Patti L; Mcdavid, Georgia E
Subject: FW: Support information.

Is Kathleen's understanding correct? Would this be true for all babies in all sites, some babies in all sites, or some babies in some sites?

From: Kennedy, Kathleen A

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Sent: Thursday, November 19, 2009 8:32 PM
To: Tyson, Jon E
Subject: Re: Support information.
As I understand it, they used a non-study sat momitor for the oxygen challenge so that was done the same way in both groups. The difference between the O2 sat groups was that the criteria for deciding who qualified for the challenge were based on the amount of O2 needed to achieve the study targets. Presumably babies in the high sat group would be more likely to get a challenge, and therefore slightly more likely to fail, than babies in the low sat group.
Kathleen A. Kennedy, MD, MPH
Director, Neonatal-Perinatal Division
Director, MS in Clinical Research Degree Program

From: Tyson, Jon E
To: Kennedy, Kathleen A
Sent: Thu Nov 19 18:08:44 2009
Subject: FW: Support information.
Do you understand exactly what she is saying? What are the implications?

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Tate, Patti L
Sent: Thursday, November 19, 2009 10:09 AM
To: Kennedy, Kathleen A
Cc: Tyson, Jon E; Mcdavid, Georgia E
Subject: Support information.

Kathleen, In the MOP on page 16-1 it states that the information is collected through 36 weeks and on page C-1 we used the BPD MOP for the reduction. We took the Masimo off the patients the day after their 36 week date then according to the BPD MOP we did the reduction if they qualified within 1 week. Therefore the information to determine if the patient qualified for the reduction was from the Masimo on the 36 week date and the reduction was done using the saturations from the unit monitors within a week. Please let me know if you have any further questions. Patti

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 3:06:00 PM

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Tuesday, November 24, 2009 2:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: VOTE:SUPPORT

Rose
I vote yes for all
At some point however we do need to revisit the # of authors per site, I don't remember the current Publication policy, but the one I am familiar with did state after the RCT Subcommittee it should be one author per site. Maybe I am wrong???
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 9:44 AM
To: Pablo.Sanchez@UTSouthwestern.edu; Shankaran, Seetha; Barbara Stoll; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; 'Krisa Van Meurs'; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Bell, Edward
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
   ___ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
   ___yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
   ___yes ____ no

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I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Carlo SUPPORT Oxygen Saturation 2009-11-24 swa
Date: Tuesday, November 24, 2009 2:51:00 PM

It is accurate – NICHD may tell me not to make a recommendation, but this is stated as a caution.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 24, 2009 1:52 PM
To: Wally Carlo, M.D.
Subject: Carlo SUPPORT Oxygen Saturation 2009-11-24 swa

Wally
Stephanie fixed the authorship as well as adding the NHLBI folks and the DSMC, I will send this version through NICHD Clearance.

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT NEJM Nov 23 (2)
Date: Tuesday, November 24, 2009 2:00:00 PM
Attachments: SUPPORT NEJM Nov 23 (2).doc

Can you add NHLBI and DSMC to this one and check the authors?

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT, CCRC[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Namasivayam Ambalavanan, MD[2], Kurt Schibler[8]; Edward Donovan[8]; Vivek Narendran, MD MRCP[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Vineet Bhandari, MD, DM[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta,

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GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]University of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were to be intubated in the delivery room and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the need for supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (CI 0.82, 1.01), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone, whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce subsequent neurodevelopmental impairment.[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with respiratory distress documenting a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[4,5,6,7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11]. There was a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

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The SUPPORT trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants would result in an increased survival without BPD at 36 weeks using the physiologic definition compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilation begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower target SpO2 range (85% to 89%) with a higher more conventional target SpO2 range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent obtained. The infants were randomized within

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each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR. CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant

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patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment because this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for

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attrition after discharge and before follow-up. Using a conservative 2% level of significance to account for the co-primary outcome of death or severe ROP in the SpO2 arm of this factorial trial, this resulted in a required sample size of 1310 infants. This sample size was not powered to detect an interaction effect between the 2 factorial arms.

The Physiologic Definition of BPD assigned the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314] Pre-specified secondary outcomes included the evaluation of BPD by the receipt of oxygen at 36 weeks.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided p value of less than 0.02 was considered statistically significant for the primary outcome of death or BPD. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation or epinephrine in the delivery room compared with the surfactant infants. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization.

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The post delivery room outcomes are provided in Table 3. The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified.

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD among survivors to 36 weeks post menstrual age using either the Physiologic Definition or the receipt of oxygen at 36 weeks (Table 3).

There were no significant differences overall for death in the delivery room, length of stay, or days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.011$). There were no significant differences between the groups for air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who were intubated during their nursery course ($p<0.001$). There was a reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2% vs. 13.2%, $p<0.001$) (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention or bevacizumab treatment for ROP among was not different in the CPAP compared to the surfactant infants (Table 3). While the study was not powered to detect an interaction

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between the two interventions, we prospectively agreed to evaluate such interactions and none were found.

Strata Results: 24 – 25 weeks Gestation

CPAP infants in this strata had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this strata are reported in Appendix Table A2.

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups in this strata, 10.8% vs 10.2%. (Appendix Table A3).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. In a pilot trial we found that 100% of infants of 23 weeks gestation required intubation in the delivery room, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

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Our trial differs from the recently reported trial of Morley et al[10][15] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven strategy of limited ventilation with infants who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation.[Error! Bookmark not defined.Error! Bookmark not defined.4,Error! Bookmark not defined.Error! Bookmark not defined.5,Error! Bookmark not defined.Error! Bookmark not defined.6] The infants who received surfactant were treated with a ventilation approach that was used by a majority of NRN units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an

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interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the primary outcomes. Data on survival without neurodevelopmental impairment at 18 to 22 months are currently accruing, and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the need for oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a clinically significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week stratum. While we did not postulate such a difference in the individual stratum this increased occurrence of death is cause for concern. The 565 infants in our 24 to 25 week stratum to our knowledge represent the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD or death by 36 weeks post menstrual age in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

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Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes including death in the immature stratum favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Figure 1 – Consort Diagram

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: Carlo SUPPORT Oxygen Saturation 2009-11-24 swa
Date: Tuesday, November 24, 2009 1:51:00 PM
Attachments: Carlo SUPPORT Oxygen Saturation 2009-11-24 swa.doc

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Wally
Stephanie fixed the authorship as well as adding the NHLBI folks and the DSMC, I will send this version through NICHD Clearance.

Rose

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy/death but resulted in an increase in mortality that and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3-5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of $\geq$ 92% (3.3 $\pm$ 0.3%) or $\geq$98% (5.6 $\pm$ 1.1%) than in units with lower oxygen saturation targets (1.4 $\pm$ 0.2% and 3.1 $\pm$ 0.3%, respectively).[5] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was

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27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these recent prospective observational studies, retrospective studies, or controlled studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, an increase in serious adverse effects or deaths were not reported.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies. The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent data coordinating center, approved the trial.

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Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). A similar algorithm was used to mask caregivers and separate oxygen saturations in premature infants.[17] Thus, an oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display

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value of 84% corresponds to actual values of 87 and 84-87% in the low and high target groups, respectively. The oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting performance. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmological specialists familiar with retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New

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Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following were present: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and

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gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on 36 pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and

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Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the

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two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome. Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

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This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The lower oxygen saturation targets or the use of oxygen restriction from birth in the current trial may be related to the adverse outcome.

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,23] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for

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oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.2)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk† (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value‡
Length of stay any hospital, (days) m+SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m+SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m+SE†	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m+SE†	59.8 ± 1.6	67.4 ± 1.5	0.0002
Continuous positive airway pressure, (days) m+SE†	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27

*Among survivors to discharge, transfer or one year; maximum value is 366 days

†Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks.

Figure 2. Survival curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. The median oxygen saturations were significantly lower for infants in the 85 to 89% oxygen saturation target group.

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Figure 1.

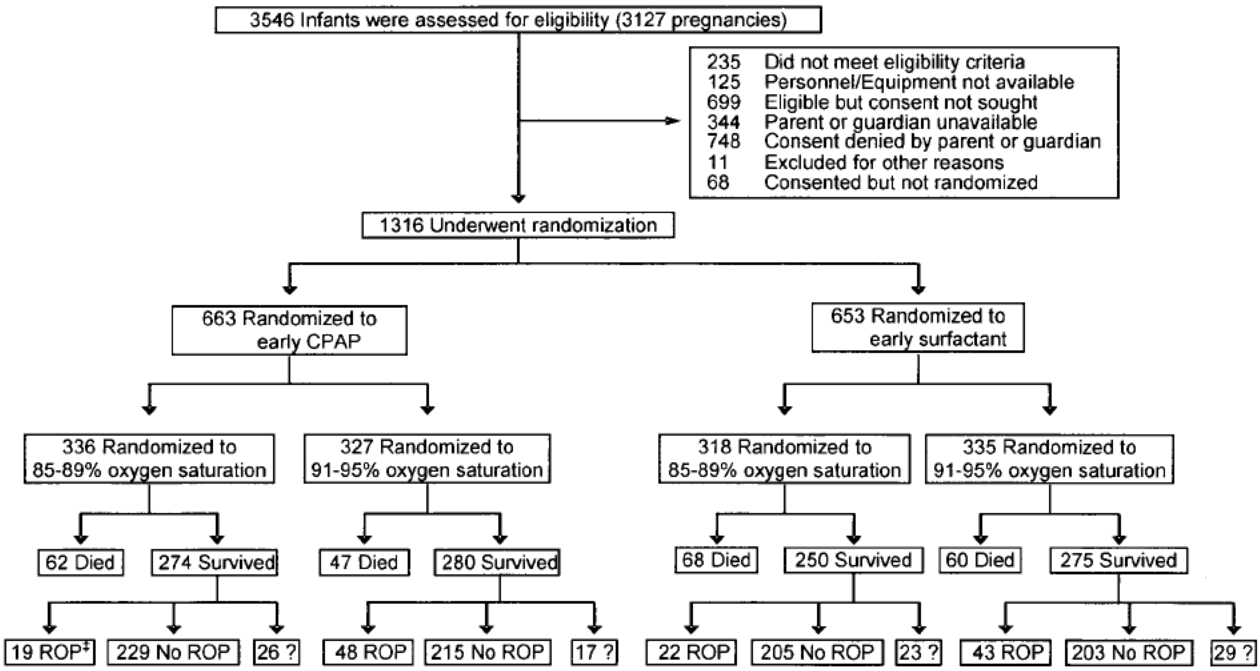

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Figure 2. Survivor Curve for Mortality

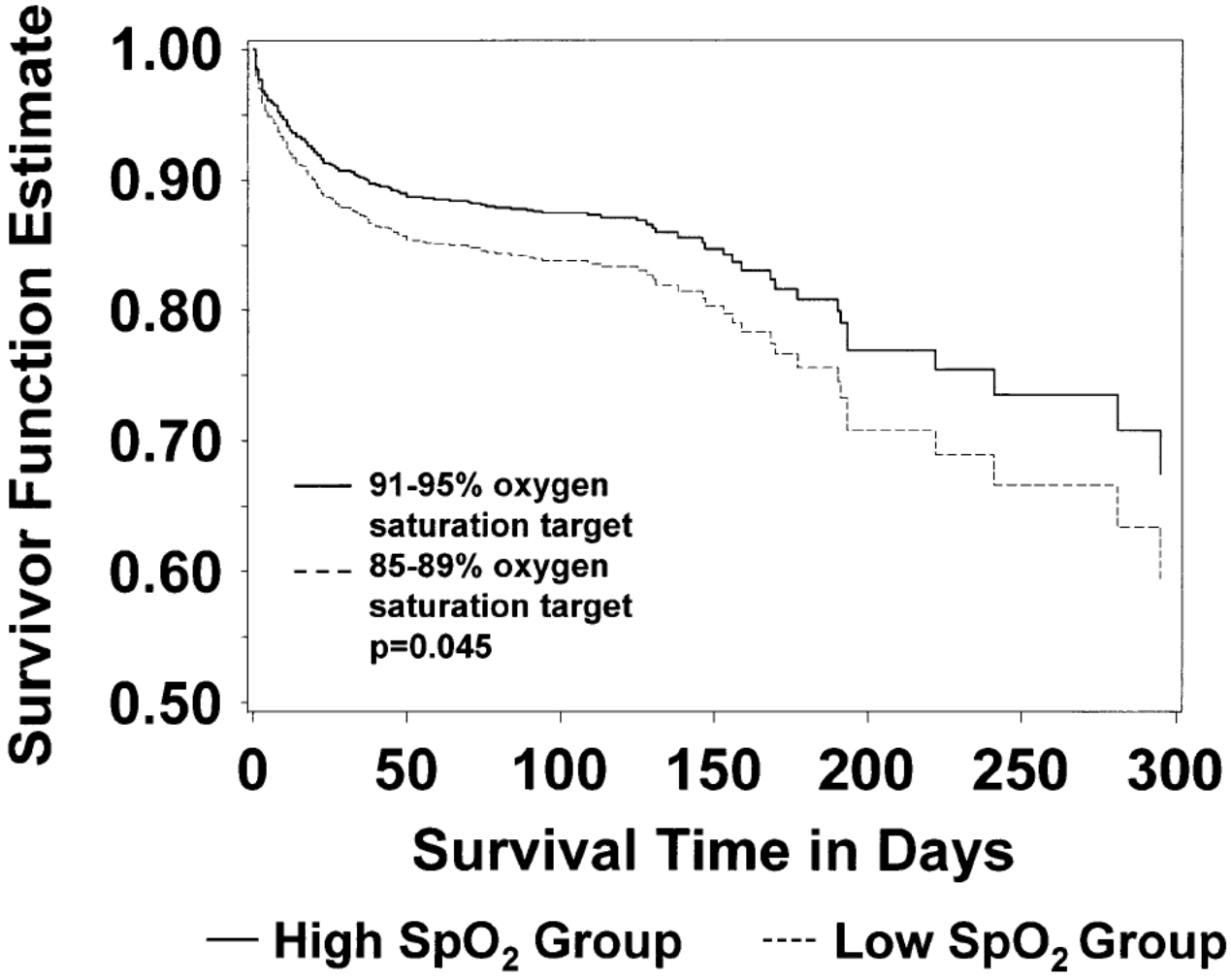

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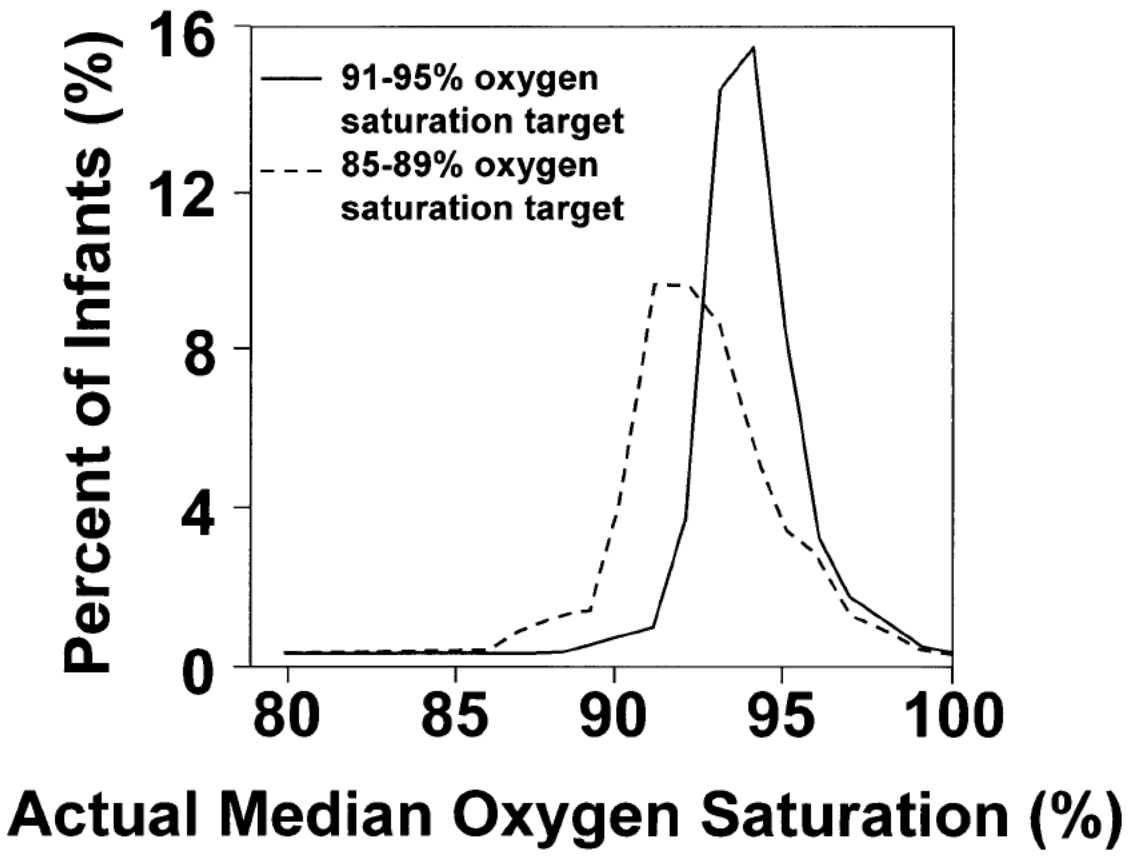
Figure 3.



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Subject: Carlo, SUPPORT Oxygen Saturation, 2009-11-24 swa.doc
Date: Tuesday, November 24, 2009 1:49:15 PM
Attachments: Carlo, SUPPORT Oxygen Saturation, 2009-11-24 swa.doc

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Here are my changes, including adding the authors (assuming they get approved).

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy/death but resulted in an increase in mortality that and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3-5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of $\geq$ 92% (3.3 $\pm$ 0.3%) or $\geq$98% (5.6 $\pm$ 1.1%) than in units with lower oxygen saturation targets (1.4 $\pm$ 0.2% and 3.1 $\pm$ 0.3%, respectively).[5] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was

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27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these recent prospective observational studies, retrospective studies, or controlled studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, an increase in serious adverse effects or deaths were not reported.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies. The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent data coordinating center, approved the trial.

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Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). A similar algorithm was used to mask caregivers and separate oxygen saturations in premature infants.[17] Thus, an oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display

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value of 84% corresponds to actual values of 87 and 84-87% in the low and high target groups, respectively. The oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting performance. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmological specialists familiar with retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New

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Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following were present: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and

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gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on 36 pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and

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Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the

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two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome. Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

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This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The lower oxygen saturation targets or the use of oxygen restriction from birth in the current trial may be related to the adverse outcome.

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,23] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for

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oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.2)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk† (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value‡
Length of stay any hospital, (days) m+SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m+SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m+SE†	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m+SE†	59.8 ± 1.6	67.4 ± 1.5	0.0002
Continuous positive airway pressure, (days) m+SE†	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27

*Among survivors to discharge, transfer or one year; maximum value is 366 days

†Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks.

Figure 2. Survival curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. The median oxygen saturations were significantly lower for infants in the 85 to 89% oxygen saturation target group.

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Figure 1.

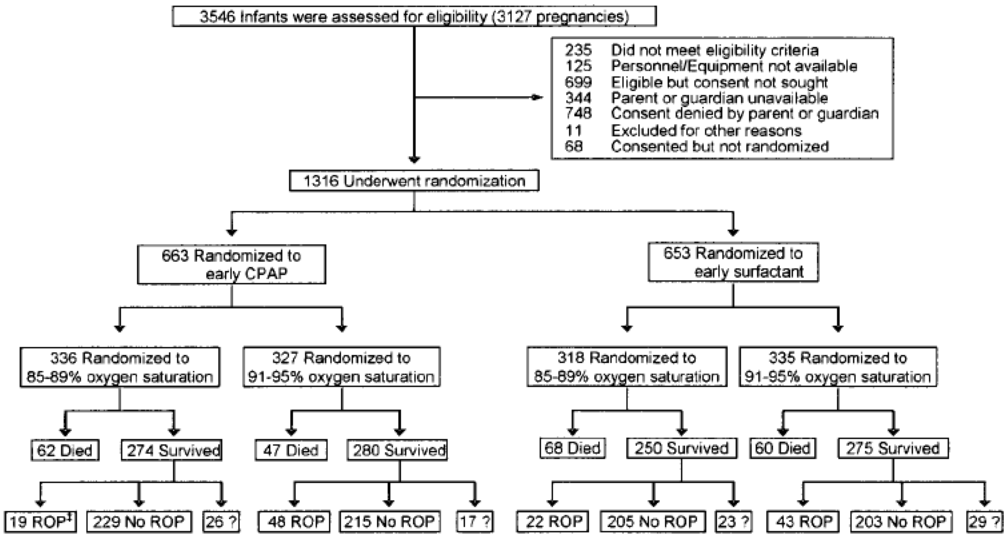

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Figure 2. Survivor Curve for Mortality

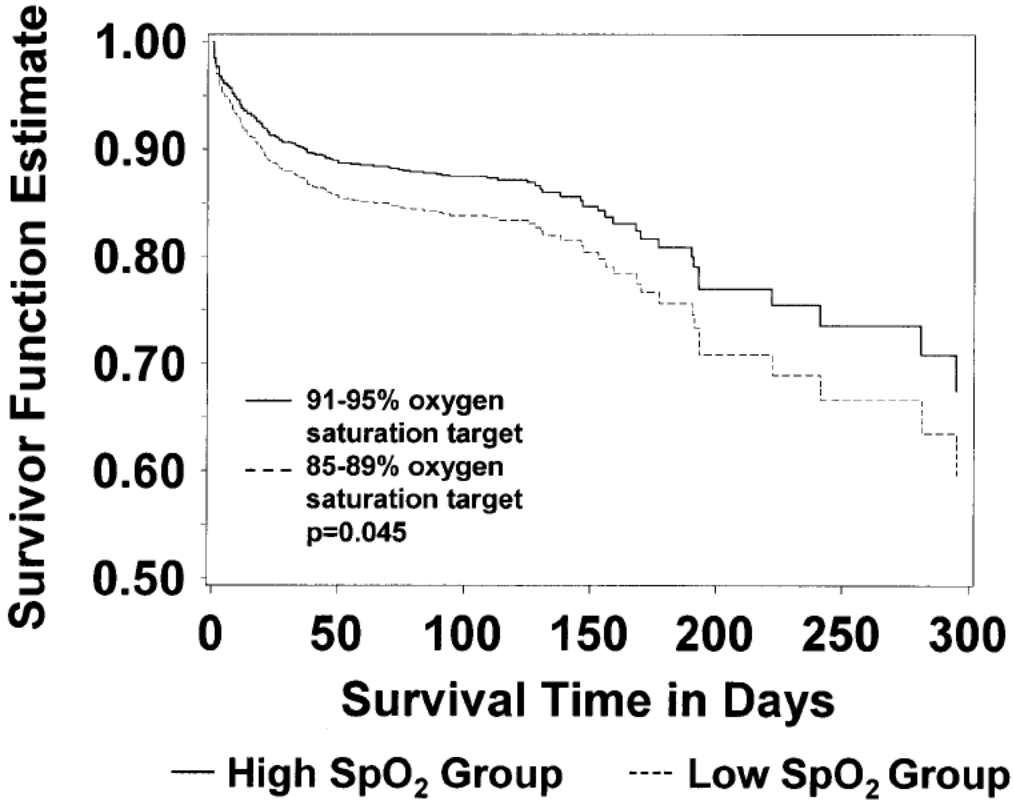

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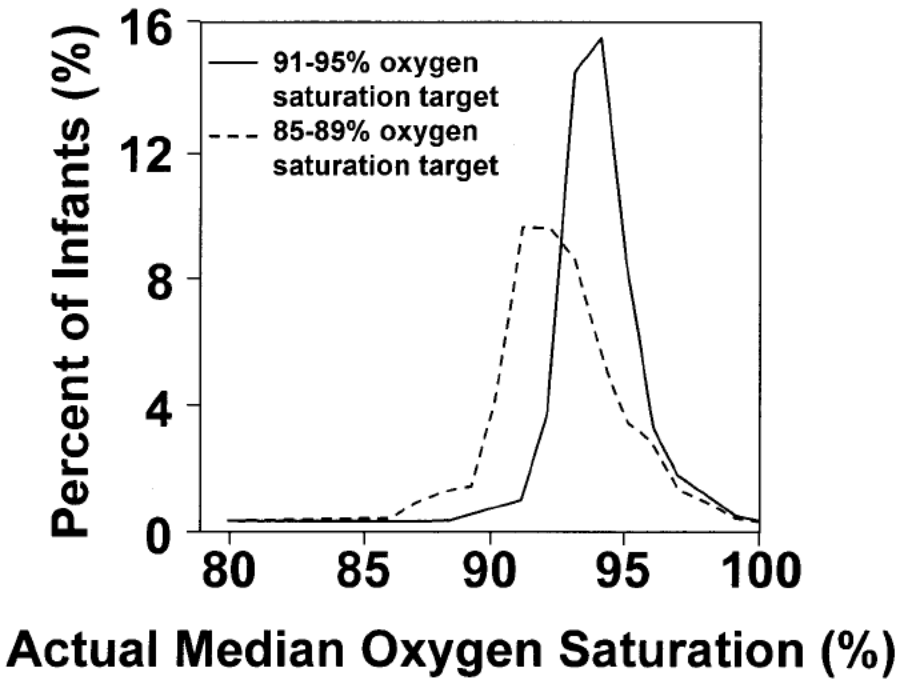
Figure 3.



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 1:21:00 PM

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, November 24, 2009 1:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: VOTE:SUPPORT

All three sound reasonable to me – so YES

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 8:44 AM
To: Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; Barbara Stoll; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; 'Krisa Van Meurs'; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Bell, Edward
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
   ___ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
   ___yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
   ___yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Oxygen Saturation Manuscript - Final?
Date: Tuesday, November 24, 2009 1:18:00 PM
Attachments: O2.Saturation.11.24.09.CLEAN.MASTER.2.doc

Can you add the NHLBI folks and the DSMC ?- he must have used an older boilerplate

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 1:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo, M.D.; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; edward.donovan@cchmc.org; Nancy Newman; IFrantz@tufts-nemc.org; susie.buchter@oz.ped.emory.edu; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Laroia, Nirupama; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; Vivek.Narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Oxygen Saturation Manuscript - Final?

Dear All:

Thanks to everyone for their comments. I have incorporated as many of your comments as possible.

Wally

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The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD, PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN, BSN.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN, MSN.

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University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN, CCRC; Erica Burnell, RN.

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Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD, MPH; Nancy J. Peters, RN, CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD, MS; Rebecca Bara, RN, BSN; Elizabeth Billian, RN, MBA.

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Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants when exposed to reduced oxygenation levels. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85-89% or 91-95%. The primary outcome was a composite of severe retinopathy of prematurity (threshold, retinopathy, surgical ophthalmologic intervention, or bevacizumab) and/or death before discharge from the hospital.

Results

The rate of severe retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001).

Conclusions

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Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of severe retinopathy/death but resulted in an increase in mortality that and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern as lower saturation targeting is increasingly being advocated to prevent retinopathy of prematurity (clinicaltrials.gov NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6,7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy,[12] and other morbidities. Although a multicenter observational study[13] could not identify an association between PaO_2 levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3-5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in neonatal intensive care units that used higher maximum oxygen saturation targets of $\geq$ 92% (3.3 $\pm$ 0.3%) or $\geq$98% (5.6 $\pm$ 1.1%) than in units with lower oxygen saturation targets (1.4 $\pm$ 0.2% and 3.1 $\pm$ 0.3%, respectively).[5] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was

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27% in units where target saturations were 88-98% and only 6% in units where the target was 70-90%.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83-95% resulted in a substantial reduction in retinopathy but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] While data from these recent prospective observational studies, retrospective studies, or controlled studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, an increase in serious adverse effects or deaths were not reported.

We conducted a 2 x 2 factorial design multicenter randomized controlled trial of two levels of oxygen saturation targeting and continuous positive airway pressure initiated in the delivery room versus intubation with surfactant using two different protocol-driven pre-defined ventilatory strategies. The oxygen saturation component of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of the composite outcome of severe retinopathy of prematurity or death among infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age at birth. The ventilation part of this factorial design trial, which was used to control the ventilatory approach and test other hypotheses, will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent data coordinating center, approved the trial.

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Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of sealed opaque envelopes to oxygen saturation targeting of 85-89% or 91-95% (the lower and higher oxygen saturation target groups, respectively) before birth using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88-92% for the targeted oxygen saturation ranges, with an offset of 3% (Masimo Radical Pulse Oximeter, Irvine, CA). A similar algorithm was used to mask caregivers and separate oxygen saturations in premature infants.[17] Thus, an oxygen saturation display of 88% corresponded to actual oxygen saturations of 85% and 91% in the 85-89% and 91-95% target groups, respectively. Likewise, an oxygen saturation display value of 92% corresponded to actual oxygen saturations of 89% and 95% in the 85-89% and 91-95% target groups, respectively. A display value of 96% corresponded to actual values of 93-96% and 96% in the low and high target groups, respectively. A display

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value of 84% corresponds to actual values of 87 and 84-87% in the low and high target groups, respectively. The oxygen saturation display transitioned and reverted to actual (non-skewed) values when less than 84% or higher than 96% in both treatment groups. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours, whichever occurred first. Infants who weaned to room air, but who subsequently received oxygen supplementation before 36 weeks post-menstrual age, were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly to each center for feedback on displayed achieved oxygen targeting performance. For the ventilation part of this 2 x 2 factorial design trial, participants were randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data collection, excluding retinopathy of prematurity examinations, was completed at discharge. All surviving infants were followed by ophthalmological specialists familiar with retinopathy of prematurity. Examinations began by 33 weeks postmenstrual age and continued until the study endpoint or resolution was reached. Threshold retinopathy of prematurity (New

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Type 1 threshold per Early Treatment of Retinopathy Cooperative Group[18,19]) was coded if any of the following findings were present:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic intervention was coded if any of the following were present: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Resolution was defined as fully vascularized retinas or immature vessels in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or severe retinopathy defined as threshold retinopathy and/or surgical ophthalmologic surgery and/or bevacizumab treatment for retinopathy. Other outcomes recorded included only predefined clinical diagnoses, including assessment of oxygen need at 36 weeks postmenstrual age[20] and safety outcomes.

Statistical analysis

The analysis for the oxygen saturation part of this factorial trial compared the percent of infants in each treatment arm who developed the primary outcome of severe retinopathy or death. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks and 95% confidence intervals. Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors. Survival analysis using Cox regression compared mortality in the low and high oxygen saturation groups. In the analysis of all outcomes, adjustment was performed as pre-specified for stratification by center and

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gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. To compare the actual oxygen saturation values in the two treatment arms, a median oxygen saturation value while on oxygen supplementation was determined for each infant. Those values were graphed by treatment group and the medians of the resulting distributions were compared using a Rank Sums test.

An absolute difference of 10% for the composite primary outcome between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or BPD in the ventilation arm of this factorial trial). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to detect, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. To account for multiple testing due to the co-primary outcomes in this factorial trial, a two-sided adjusted p value of less than 0.02 was considered to be statistically significant for the primary outcome of death or severe retinopathy. P values for secondary

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outcomes are reported descriptively at the per-test level. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned secondary outcome comparisons by treatment, we would expect no more than three tests to have a p value of less than 0.05 on the basis of chance alone. Sub-group analyses were conducted within pre-specified gestational age strata on 36 pre-defined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have p values of less than 0.05 based on chance alone.

An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

1316 infants were enrolled between February 2005 and February 2009 (Figure 1). When 247 infants had been enrolled, enrollment was temporarily paused upon recommendation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and

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Human Development Director because of concerns that displayed oxygen saturations often exceeded the targets Separation of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns because infants not requiring supplemental oxygen accounted for a large proportion of the high saturation levels maintained. Continued enrollment was approved.

The baseline characteristics of the two treatment groups were similar (Table 1). The primary outcome, severe retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; p= 0.20; Table 2). Death before discharge occurred in 130 of the 654 (19.9%) infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p= 0.04; number needed to harm 27). The distribution of the major causes of death did not differ significantly between the intervention and control groups (Appendix Table 1). Comparable results were observed for both gestational age strata. Survival analysis using Cox regression produced similar results (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Severe retinopathy among survivors to discharge, transfer, or one year was decreased in the lower oxygen saturation group (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p< 0.001; number needed to treat 11). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group (p=0.002) but bronchopulmonary dysplasia among survivors determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks did not differ significantly between the treatment groups. Other pre-specified major outcomes did not differ significantly between the

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two treatment groups (Table 2). While the trial was not powered to detect an interaction between the oxygen saturation and the ventilatory intervention, we prospectively agreed to evaluate such interactions and none were found.

The median oxygen saturation of infants in the two treatment groups while receiving oxygen supplementation differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual median oxygen saturation levels were slightly higher than targeted in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Appendix Table 2). Other measures of resource utilization did not differ as well.

DISCUSSION

In this multicenter randomized trial we found that even though lower oxygen saturation targeting reduced severe retinopathy among survivors, it also increased the risk for in-hospital mortality. Longer follow-up will be important to determine the effects on functional visual outcome. Despite the absence of recent randomized trials and safety data and the increase in mortality when a restrictive oxygen supplementation was tested and practiced in the 1950s and 1960s, lower oxygen saturation targeting with the goal of reducing retinopathy of prematurity is becoming common practice.[3-5,15,16,21]

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This is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results, in conjunction with previous reports, add to the concern that oxygen restriction may increase mortality in preterm infants. It is interesting and worrisome that the combined risk difference observed in the trials from the 1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.7% mortality increase in the lower oxygen saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17,22] However, these trials aimed for saturations of 91-94% and 89-94% in the lower oxygen saturation group, which are closer to the targets of the higher saturation arm in the current trial. The lower oxygen saturation targets or the use of oxygen restriction from birth in the current trial may be related to the adverse outcome.

Meta-analyses of restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,23] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth. However, like most non-randomized studies[3-5,15,16], our trial confirmed that lower oxygen saturation targeting results in a large reduction of severe retinopathy among survivors.

There are several ongoing trials across the world that address the same intervention tested in the current trial and a planned prospective meta-analysis.[24] These trials use the same algorithm for

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oxygen saturation targeting so their data will be combined in a meta-analysis to determine short and long term effects of oxygen saturation targeting.

In summary, oxygen saturation targeting in the 85-89% range did not affect the combined outcome of severe retinopathy/death but it increased mortality while substantially decreasing severe retinopathy among survivors. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years, but at the present time, caution should be exercised regarding oxygen targeting for premature infants in the low range tested as it may lead to increased mortality.

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Table 1. Baseline Characteristics of the Patients in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Characteristic	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight – g (m±SD)	836±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)	279/662 (42.1)
Black (non-Hispanic)	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other/unknown	23/654 (3.5)	24/662 (3.6)
Antenatal corticosteroids (any) – no. (%)	633/654 (96.8)	632/661 (95.6)
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)	462/658 (70.2)
5-min Apgar score < 3 – no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant – no. (%)	531/653 (81.2)	558/660 (84.5)

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Table 2. Major Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk[†] (95% CI)
Severe retinopathy/death	170/605 (28.1)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe retinopathy	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84, 1.70)
Death by 36 weeks post-menstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)	331/662 (50.0)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)
Cystic periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)
Cystic periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)

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Surgical treatment for patent ductus arteriosus	73/641 (11.4)	68/648 (10.5)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7.1)	43/662 (6.5)	1.12 (0.74, 1.68)
Any air leaks in the first 14 days – no. (%)	51/654 (7.8)	42/662 (6.5)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)

*In babies alive at 36 weeks post-menstrual age.

†Adjusted for stratification factors (study center and GA group) as well as for familial clustering

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Appendix Table 1: Cause of Death in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Category – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)
Respiratory distress syndrome	31/130 (23.8)	31/107 (29.0)
Infection	25/130 (19.2)	21/107 (19.6)
Necrotizing enterocolitis	23/130 (17.7)	14/107 (13.1)
Bronchopulmonary dysplasia	14/130 (10.8)	10/107 (9.3)
Central nervous system insult	12/130 (9.2)	9/107 (8.4)
Immaturity	7/130 (5.4)	3/107 (2.8)
Other	18/130 (13.8)	19/107 (17.8)

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Appendix Table 2. Other Outcomes in a Randomized Trial of Lower versus Higher Oxygen Saturation Targets in Extremely Low Birth Weight Infants

Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P value‡
Length of stay any hospital, (days) m+SE*	104.5 ± 2.0	106.4 ± 2.0	0.45
Length of stay at study hospital, (days) m+SE*	99.8 ± 2.0	103.0 ± 2.0	0.22
Duration of mechanical ventilation, (days) m+SE†	25.5 ± 1.1	26.9 ± 1.0	0.30
Duration of oxygen supplementation, (days) m+SE†	59.8 ± 1.6	67.4 ± 1.5	0.0002
Continuous positive airway pressure, (days) m+SE†	17.1 ± 0.6	17.0 ± 0.6	0.94
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†	3.3 ± 0.3	3.8 ± 0.3	0.14
Alive off mechanical ventilation by day 14, (days) – no. (%)	332/644 (51.6)	326/655 (49.8)	0.86
Alive off mechanical ventilation by day 7, (days) – no. (%)	351/648 (54.2)	329/659 (49.9)	0.27

*Among survivors to discharge, transfer or one year; maximum value is 366 days

†Among survivors to discharge, transfer or 120 days; maximum value is 120 days

‡Adjusted for stratification factors (study center, gestational age group) as well as for familial clustering

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Legends

Figure 1. Flow chart of the screening, random assignment, and primary outcome. ROP denotes retinopathy of prematurity. The numbers excludes pregnancies screened which did not subsequently result in a birth at a study center at $24^{0/7}$ to $27^{6/7}$ weeks.

Figure 2. Survival curve for mortality. Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (hazard ratio 1.32; CI 1.01, 1.72; p= 0.045).

Figure 3. Median actual oxygen saturations while on oxygen supplementation for infants in each of the treatment groups. The median oxygen saturations were significantly lower for infants in the 85 to 89% oxygen saturation target group.

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Figure 1.

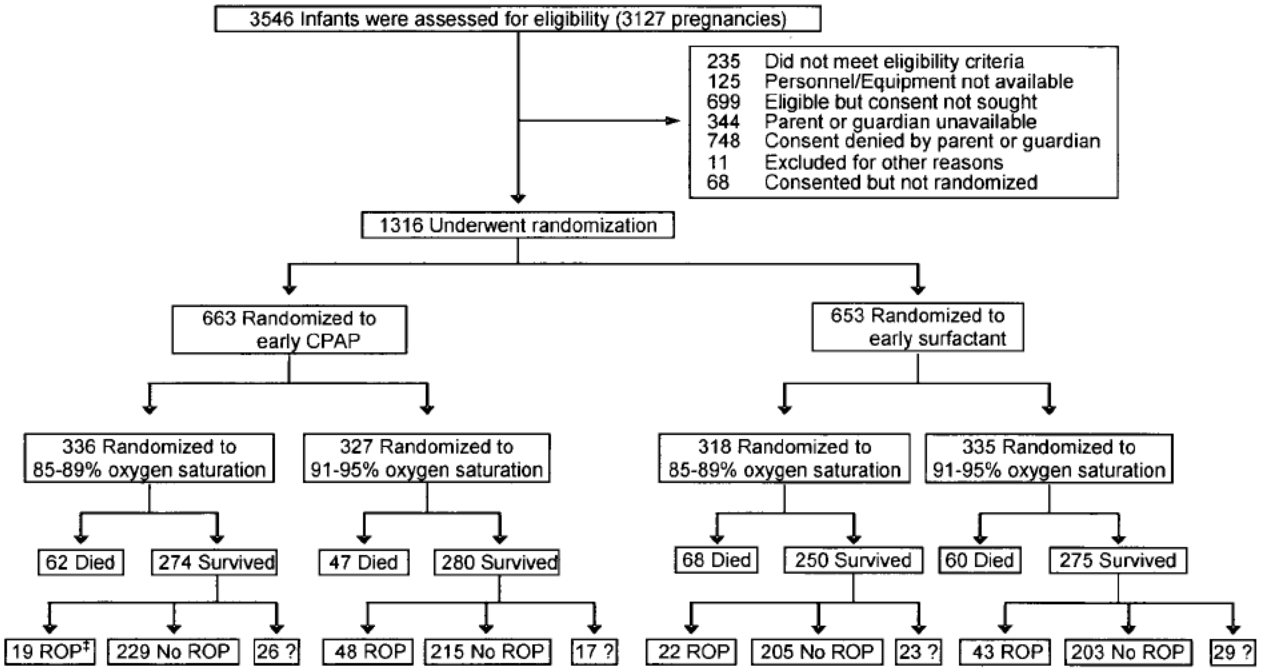

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Figure 2. Survivor Curve for Mortality

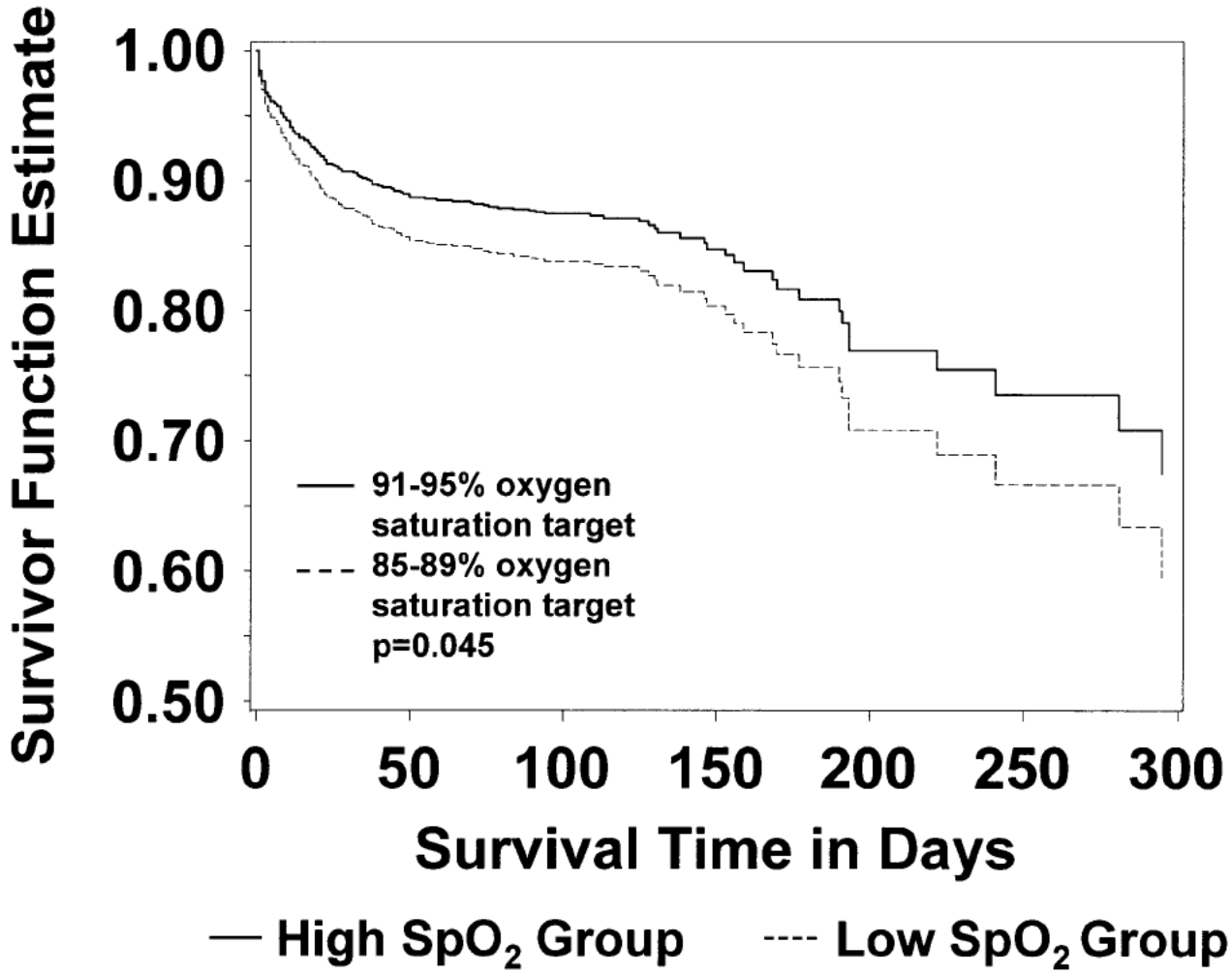

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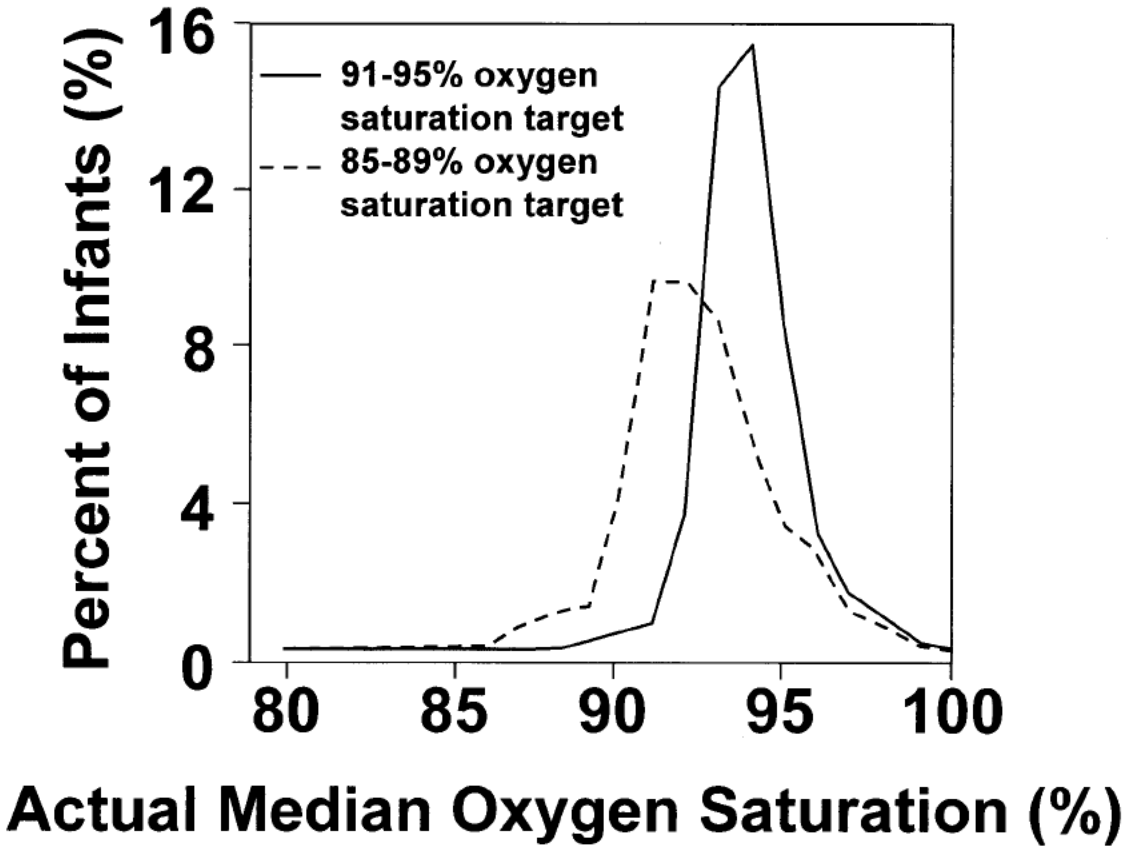
Figure 3.



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 12:20:00 PM

-----Original Message-----
From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Tuesday, November 24, 2009 12:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: VOTE:SUPPORT

Yes for all 3.
Richard

Higgins, Rosemary (NIH/NICHD) [E] wrote:
>
> For the SUPPORT manuscripts, there are three requests for authorship
> which have been approved by the SUPPORT Subcommittee:
>
> 1. For Alabama, Ambal is requested to be an author
> based on his pivotal role in the trial at the highest recruiting site.
>
> __X_ yes ___no
>
> 2. For Rochester, Dale Phelps is recommended to be
> added to the oximetry paper due her role in training for ROP and
> source of ROP advice during the trial.
>
> __X_yes ____no
>
> 3. For Cincinnati, Ed Donovan is recommended to be
> added to the CPAP paper for his role in trial training and serving on
> the subcommittee until Kurt took over in 2006.
>
> __X_yes ____ no
>
> I am sending this email to the non-SUPPORT subcommittee members for
> input as the SUPPORT SUBCOMMITTEE has already voted.
>
> Please respond by November 25
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal Medicine
>
> Eunice Kennedy Shriver National Institute of Child Health and Human

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"; "Wally Carlo, M.D."; "Gantz, Marie"; "Das, Abhik"
Subject: RE: Support information.
Date: Tuesday, November 24, 2009 12:17:00 PM

I looked and could not find one – perhaps the coordinator's minutes??

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 24, 2009 12:09 PM
To: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

We are looking for a technical memo on this – do any of you know of such a memo??
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 8:18 AM
To: Gantz, Marie; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

I agree. But Jon says that their RNs used the altered oximeters to determine the need for the phys test

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, November 24, 2009 10:12 AM
To: Wally Carlo, M.D.; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support information.

How did they know whether the baby had majority saturation >=90% based on the altered oximeters? An actual saturation of 90% would have corresponded to a display value of 87 or 93 depending on whether the low or high oximeter was used.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 24, 2009 11:08 AM
To: Gantz, Marie; Das, Abhik; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Support information.

This is what I got from Monica but we should try to find if we have some official documentation of this.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Monica Collins
Sent: Tuesday, November 24, 2009 9:58 AM
To: Wally Carlo, M.D.
Subject: RE: Support information.

It was decided based on their status at 36 weeks--they were on the Massimos at that time. However, as part of the physiologic reduction, all babies were put on a unit (nonblinded, nonskewed) oximeter for a baseline period, then reduced if continuing to meet the criteria for reduction. There should have been no difference in failure rate in the babies who were in the high sat group vs. the low sat group.
Monica

From: Wally Carlo, M.D.
Sent: Mon 11/23/2009 6:12 PM
To: Monica Collins; Shirley Cosby
Subject: FW: Support information.

Monica and Shirley:

Did we decide on the need for physiologic test based on the study oximeter or the regular one?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Monday, November 23, 2009 6:01 PM
To: Wally Carlo, M.D.
Cc: Kennedy, Kathleen A
Subject: FW: Support information.

Here is the info I got. Is it incorrect?

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Mcdavid, Georgia E
Sent: Monday, November 23, 2009 1:38 PM
To: Tate, Patti L; Tyson, Jon E
Cc: Kennedy, Kathleen A
Subject: RE: Support information.

Are we all clear about this? The study oximeter was in place on the 36 week date (we removed it the next day). Whether or not an infant is reduced using the Physiologic Definition is determine by the effective oxygen on that 36 week day. We had a week after the 36 week date to perform the physiologic definition.

From: Tate, Patti L
Sent: Friday, November 20, 2009 10:54 AM
To: Tyson, Jon E
Cc: Kennedy, Kathleen A; Mcdavid, Georgia E
Subject: RE: Support information.

Dr. Tyson, I believe that Dr. Kennedy's assessment is correct. All the centers should have done it the same way. The Masimo oximeter stayed on the infant through the 36 week date and BPD criteria is on the 36 week date. The reduction is to be done within 1 week of the 36+1 week date. 1. Oxygen by NC <27% effective oxygen and the majority of saturations greater than or equal to 90% in the prior 24 hours is eligible for reduction. 2. Oxygen by NC 27-30% effective oxygen and the majority of saturations greater than or equal to 96% in the prior 2 hours are eligible for reduction. 3. Room air NC at any liter flow is eligible for reduction. The Masimo oximeters displayed a target of 88-92% on both the high and low range altered oximeters. Low range was actual 85-89% target and the high range was actual 91-95% target. Since the study monitor was removed from the infant on the 36+1 date the reductions were done on the unit monitors and this should be consistent with all the centers. I have the MOP in the office of both the Support and BPD if you need them. I hope that this helps.

From: Tyson, Jon E
Sent: Friday, November 20, 2009 5:41 AM
To: Tate, Patti L; Mcdavid, Georgia E
Subject: RE: Support information.

Can we be really sure that % in room air at 36 wks was not influenced by study monitor? Can you

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forward me the MOP, tell me what page to look at, and let's discuss by phoen or in person?

From: Tyson, Jon E
Sent: Friday, November 20, 2009 5:05 AM
To: Tate, Patti L; Mcdavid, Georgia E
Subject: FW: Support information.

Is Kathleen's understanding correct? Would this be true for all babies in all sites, some babies in all sites, or some babies in some sites?

From: Kennedy, Kathleen A
Sent: Thursday, November 19, 2009 8:32 PM
To: Tyson, Jon E
Subject: Re: Support information.

As I understand it, they used a non-study sat momitor for the oxygen challenge so that was done the same way in both groups. The difference between the O2 sat groups was that the criteria for deciding who qualified for the challenge were based on the amount of O2 needed to achieve the study targets. Presumably babies in the high sat group would be more likely to get a challenge, and therefore slightly more likely to fail, than babies in the low sat group.
Kathleen A. Kennedy, MD, MPH
Director, Neonatal-Perinatal Division
Director, MS in Clinical Research Degree Program

From: Tyson, Jon E
To: Kennedy, Kathleen A
Sent: Thu Nov 19 18:08:44 2009
Subject: FW: Support information.

Do you understand exactly what she is saying? What are the implications?

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Tate, Patti L
Sent: Thursday, November 19, 2009 10:09 AM
To: Kennedy, Kathleen A
Cc: Tyson, Jon E; Mcdavid, Georgia E
Subject: Support information.

Kathleen, In the MOP on page 16-1 it states that the information is collected through 36 weeks and on page C-1 we used the BPD MOP for the reduction. We took the Masimo off the patients the day after their 36 week date then according to the BPD MOP we did the reduction if they qualified within 1 week. Therefore the information to determine if the patient qualified for the reduction was from the Masimo on the 36 week date and the reduction was done using the saturations from the unit monitors within a week. Please let me know if you have any further questions. Patti

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 12:16:00 PM

-----Original Message-----
From: Krisa Van Meurs [mailto:vanmeurs@stanford.edu]
Sent: Tuesday, November 24, 2009 11:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: VOTE:SUPPORT

>For the SUPPORT manuscripts, there are three requests for authorship
>which have been approved by the SUPPORT Subcommittee:
>1. For Alabama, Ambal is requested to be an author
>based on his pivotal role in the trial at the highest recruiting
>site.
>_x__ yes ___no
>2. For Rochester, Dale Phelps is recommended to be
>added to the oximetry paper due her role in training for ROP and
>source of ROP advice during the trial.
>_x__yes ____no
>3. For Cincinnati, Ed Donovan is recommended to be
>added to the CPAP paper for his role in trial training and serving
>on the subcommittee until Kurt took over in 2006.
>__x_yes ____ no
>I am sending this email to the non-SUPPORT subcommittee members for
>input as the SUPPORT SUBCOMMITTEE has already voted.
>Please respond by November 25
>Thanks
>Rose
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
>Eunice Kennedy Shriver National Institute of Child Health and Human
>Development
>National Institutesof Health
>6100 Executive Blvd., Room 4B03
>MSC 7510
>Bethesda, MD 20892
>For overnight delivery use Rockville, MD 20852
>301-496-5575
>301-496-3790 (FAX)
>higginsr@mail.nih.gov
>

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, November 24, 2009 12:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.

Rose
I generally stay away from any discussion about authors, but I have a concern as to why there are 3 authors for Cincinnati.
Is there a reason?
I believe that I have had input from Kurt. In any case I do not support 3 PIs from one center unless they were the lead unit (Wally was) or there was some other mitigating situation. Many of the main PIs are not on the author list.
Can we change this??
Thanks
Neil

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wrich@ucsd.edu"
Subject: Antenatal_Consent_Paper_Network_Final (2)
Date: Tuesday, November 24, 2009 11:54:00 AM
Attachments: Antenatal_Consent_Paper_Network_Final (2).doc

Wade
there were a few minor comments in the clearance process about a steroid Cochrane reference and the term "under privileged. please send me an amended version so I can complete the clearance

Thanks
Rose

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Antenatal Consent in a Large Multicenter Trial - At What Cost?

Wade Rich, BSHS, RRT[1]; Kathy J. Auten, MSHS[2]; Marie Gantz, PhD[3]; Ellen C. Hale, RN BS CCRC[4], Angelita M. Hensman, RN BSN[5], Nancy S. Newman, RN[6], and Neil N. Finer, MD[1] for the NICHD Neonatal Research Network

[1] University of California at San Diego, San Diego, CA

[2] Department of Pediatrics, Duke University, Durham NC

[3] RTI International, Research Triangle Park, NC

[4] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA

[5] Department of Pediatrics, Women & Infants' Hospital, Brown University, Providence, RI

[6]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

Short title: Antenatal Consent in a Large Multicenter Trial

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Keywords: Informed Consent, Antenatal, Neonatal

The authors have no financial disclosures or conflicts of interest.

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

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University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

ABSTRACT

Background

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

The purpose of this study was to quantify the time, effort, and rate of success involved obtaining antenatal consent to enroll infants into the Neonatal Research Network SUPPORT trial, and to determine if these infants were representative of the eligible population.

Methods

Eligible subjects were those likely to deliver in the SUPPORT gestational age window (24-27 6/7 wks). Data included who approached them for consent, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled in the trial. In addition, all eligible, non-enrolled infants entered into the NRN Generic Database (GDB) throughout the period of SUPPORT enrollment were identified to allow comparison of all infants enrolled in SUPPORT to those who were eligible but not enrolled.

Results

2826 women were identified at 18 sites between October 2005 and February 2009. 2228 were approached for consent and 1219 (54.7%) agreed. For 76.9% of those approached, < 3 visits were required to complete the consent process. (mean 2.0 +/- 1.2). Of the 659 consented infants delivered within the study window, 611 of were enrolled. Mothers who received a neonatal consult were more likely to give consent ($p<.001$). Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached (n=2290) to those whose mothers were approached (n=2082), the percentage of infants not exposed to steroids was significantly greater in the non-approached vs. the approached group (20.0%, 3.4% $p<.001$).

Conclusions:

In a trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver in the GA window for each one who delivered an enrolled infant. The differences between enrolled and non-enrolled infants highlight difficulties in attempting to recruit a representative population for trials requiring antenatal consent.

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Introduction:

Informed consent ensures that subjects enrolled in research trials are appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery.

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation in which a site is paid based on the number of subjects enrolled. Funds may be awarded for screening for eligible subjects, but centers are not usually paid for the time required to seek or obtain consent for subjects who are not enrolled. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

The early months of enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that the number of patients enrolled seemed to be much lower than the number screened. Thus, this secondary study was designed to quantify the antenatal screening and consent process to determine the time, effort and other factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network. The second objective of the study was to determine whether the subjects enrolled in the trial were representative of the overall eligible population.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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second half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early Continuous Positive Airway Pressure (CPAP) initiated in the delivery room to early intubation and surfactant given within the first hour of life, in a 2x2 factorial design with randomization to two different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were those inborn at NRN centers at 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was planned. SUPPORT enrollment began in February 2005 and ended in February 2009.

Eligible subjects for the antenatal consent secondary study were those women whom the Obstetrical/Perinatal staff thought were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (RTI International, Research Triangle Park, NC). Research staff collected study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts that were made by the research coordinator/RN, and whether permission from the obstetrician was obtained to approach for antenatal consent. Because a neonatal consult is often performed as part of clinical management in this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached were asked if they were asked to participate in any other studies for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the Data Coordinating Center. As part of the ongoing NRN Generic Database (GDB) observational

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study, data were routinely collected on inborn infants at NRN centers, including most of those who met the gestational age eligibility criteria for the SUPPORT study. These data were used to identify eligible non-enrolled (non-consented) infants and to evaluate whether infants enrolled in the SUPPORT trial represented the eligible NRN population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment met enrollment criteria for participation in SUPPORT. Eligible but non-enrolled infants had information collected on prenatal care, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT. These data were used to determine whether all eligible women were approached and if not, what the reasons for not approaching them were.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2826 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two NRN centers did not participate in the antenatal consent trial and 4 participating centers did not identify 50 eligible women who delivered in the GA window between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Thirteen centers had more than 50 women deliver in the GA window (range 51 to 90) before they stopped collecting data. All data collected by participating centers have been included in this analysis. Analysis

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using only the first 50 women from the centers that over-enrolled was not significantly different. Screening, enrollment and consent numbers by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Mothers were considered unable to give consent when in active labor, too young, or having either a mental or physical health issue which precluded them being approached.

A study coordinator or research RN made 74.7% of all approaches. For 76.9% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1219 (54.7%) gave consent, and 581 subsequently delivered within the SUPPORT study window. Of these, 536 delivered infants who were enrolled (Figure 2). Forty-eight of the 659 consented infants born in the GA window (7.3%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 69.7% of cases where the parent(s) were approached for consent. Mothers receiving a neonatal consult were more likely to consent ($p < .001$), but consent was obtained during the consult in only 11.6%.

Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose mothers were approached revealed several important differences (Table 2). Infants of approached mothers were significantly more likely to be non-Hispanic white; to be older, and to have a high school education , private medical insurance, and at least one PNC visit. A significantly higher proportion of eligible infants whose mothers were not approached had no exposure to antenatal

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steroids compared with infants whose mothers were approached (20.0% vs 3.4%, p<.001). Maternal parity was lower in women who were approached, but gravidity was not significantly different between the groups.

Eligible GDB infants who were not enrolled in SUPPORT and those who were enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance and to have received prenatal care and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%) (Table 3).

Discussion:

To our knowledge this is the first study to evaluate the time and efforts required to approach and obtain antenatal consent from parents for the enrollment of their unborn infants. Our results reveal that 5 families needed to be identified and screened for every one infant successfully enrolled. Only 47.7% of women consented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.6) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.6 hours. Assuming that the enrollment rate of the SUPPORT trial was equivalent before data collection for the antenatal consent study began suggests that over 2400 hours were spent screening greater than 6000 women and approaching nearly 4800 for consent to enroll 1316 infants in the SUPPORT trial. This estimate includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found

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that only 8.4% of women reported having been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT gestational age window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. The approached vs. non-approached data help us to better understand what part of the population never had an opportunity to be part of the enrollment, and what the reasons were. The enrollment data allow us to compare the population that was enrolled in the trial with those who were eligible but not enrolled. This is the ultimate result of the consent process.

Infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants.[1,2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

Comment [h1]: The 2 does not refer to the consent, but rather to the steroids themselsve. Recommendation to split this sentence into 2 sentences.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which collected data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items.[4,5] The standards require a flow chart of participants to quantify eligible populations but it does not require identifying the demographics of the non-enrolled group or its similarity to the enrolled or consented populations. Following the CONSORT standards in all antenatal consent trials, that is, obtaining basic demographic information for all eligible infants, will help us understand whether similar reduction biases in enrollment occurs in other studies.

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Blinding of allocation has always been the benchmark for protecting trials from biased enrollment. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[6] However, these controls only protect the trial from internal bias, not the selection bias we have seen. It does not affect the external validity or generalizability of the findings to non-study patients. Manning and Silverman have voiced concerns about this type of selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[7,8] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [9] In a study of recruitment and retention of premature infants into an early intervention trial, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [10,11] In our study, the sociodemographic variables tended to favor the enrolled group. Mitchell and Kline showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13] In our study, the socio-demographic variables tended to favor the enrolled group.

Our analysis would suggest that under-privileged subjects were less likely to participate. Because this trial included subjects from 18 academic centers with long-term experience in randomized trials and a broad mix of racial, ethnic, and socio-economic populations, it is not likely that the bias represents an intention to include or exclude any group. The logical conclusion is that the many subjects who were not enrolled in this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[14], suggest that it may be ethically appropriate to allow trials that compare routinely used interventions to waive

Comment [h2]: You may wish to use more exact terms such as self pay/uninsured. Also, those who were approached were more likely to have a high school education than those not approach!!

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the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population enrolled as a result of antenatal consent may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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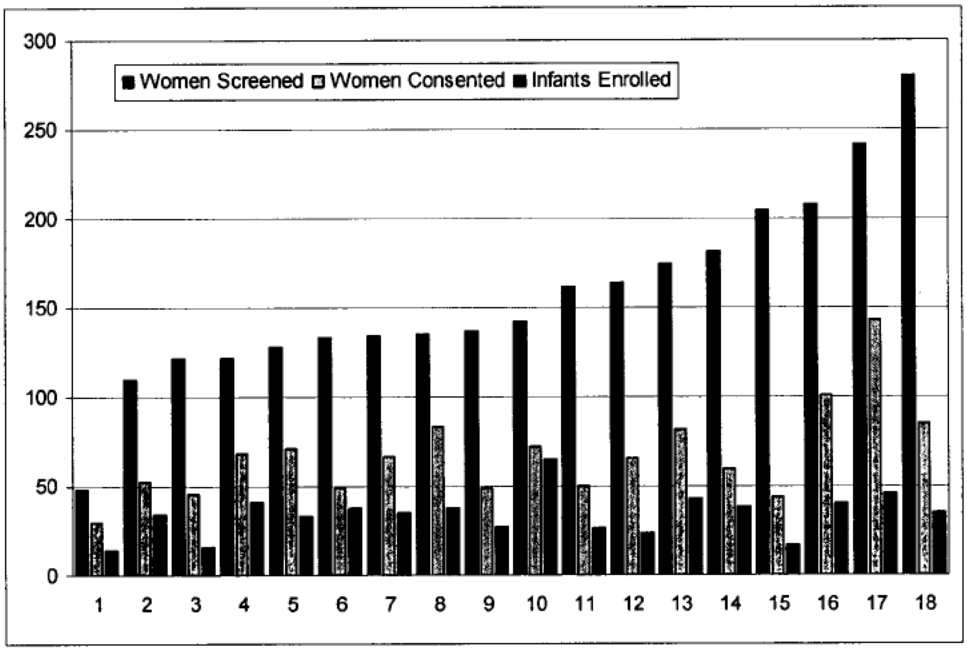

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.5
Insufficient time	119	19.9
Study staff unavailable	37	6.2
Consult not done	17	2.8
Not aware of admission	35	5.9
Other	321	53.7

Table 1. Reasons for not approaching mothers for consent.

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	Infants whose Mothers were Approached N=2082	Infants whose Mothers were Not Approached N=2290	p Value
Maternal age (Mean ± SD)	27.5 ± 6.4	26.9 ± 6.8	0.0071
White-Non Hispanic	853 (41.0%)	774 (33.9%)	<0.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0844
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0463
≥ HS Education	1134 (75.3%)	1090 (68.3%)	<0.0001
Self Pay/Uninsured	130 (6.3%)	228 (10.0%)	<0.0001
At Least 1 PN Visit	2015 (96.8%)	2112 (92.4%)	<0.0001
No Antenatal Steroids	71 (3.4%)	457 (20.0%)	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Enrolled Infants N=1316	Non-Enrolled Infants N=3056	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.2 ± 6.7	0.7107
White-Non Hispanic	521 (39.7%)	1106 (36.3%)	0.0329
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9438
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7725
≥ HS Education	708 (74.1%)	1516 (70.61%)	0.0490
Self Pay/Uninsured	81 (6.2%)	227 (9.1%)	0.0012
At Least 1 PN Visit	1263 (96.0%)	2864 (93.9%)	0.0052
No Antenatal Steroids	50 (3.8%)	478 (15.7%)	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

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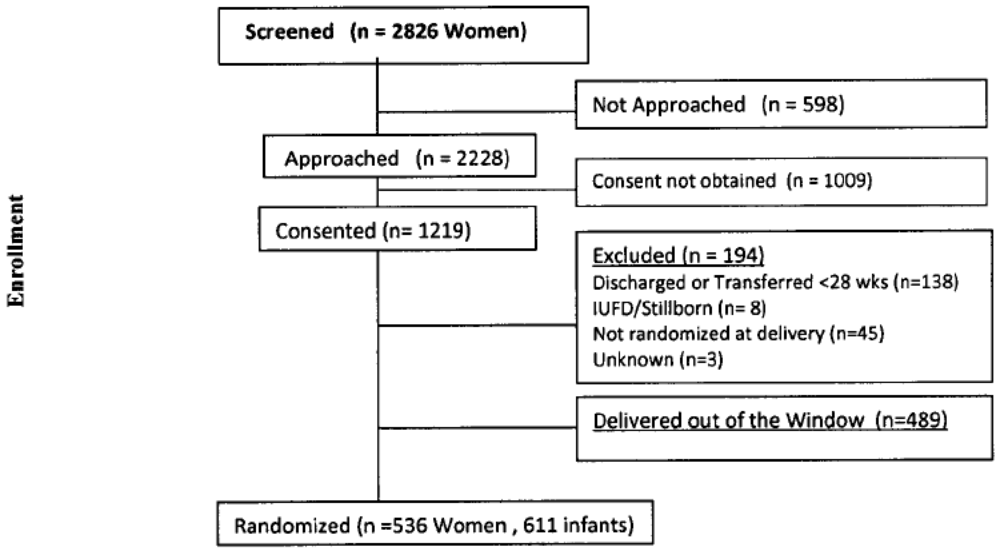

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 11:49:53 AM

>For the SUPPORT manuscripts, there are three requests for authorship
>which have been approved by the SUPPORT Subcommittee:
>1. For Alabama, Ambal is requested to be an author
>based on his pivotal role in the trial at the highest recruiting
>site.
>_x__ yes ___no
>2. For Rochester, Dale Phelps is recommended to be
>added to the oximetry paper due her role in training for ROP and
>source of ROP advice during the trial.
>_x__yes ____no
>3. For Cincinnati, Ed Donovan is recommended to be
>added to the CPAP paper for his role in trial training and serving
>on the subcommittee until Kurt took over in 2006.
>__x_yes ____ no
>I am sending this email to the non-SUPPORT subcommittee members for
>input as the SUPPORT SUBCOMMITTEE has already voted.
>Please respond by November 25
>Thanks
>Rose
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
>Eunice Kennedy Shriver National Institute of Child Health and Human
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>MSC 7510
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 10:24:30 AM

From: Frantz, Ivan <ifrantz@tuftsmedicalcenter.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 24 10:19:50 2009
Subject: RE: VOTE:SUPPORT

Yes to all.

Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 9:44 AM
To: Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; Barbara Stoll; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; 'Krisa Van Meurs'; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; Frantz, Ivan; Bell, Edward
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
   ___ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
   ___yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
   ___yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch

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From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP
Date: Tuesday, November 24, 2009 10:11:53 AM

Yes!!

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 11:04 AM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Bradley Yoder; Roger Faix; Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: VOTE:SUPPORT
Date: Tuesday, November 24, 2009 9:45:00 AM

Use the SUPPORT subcommittee votes for the PI's on the subcommittee

---

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, November 24, 2009 9:45 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: VOTE:SUPPORT

Yes to all

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 24, 2009 9:44 AM
To: Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; Barbara Stoll; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; 'Krisa Van Meurs'; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Bell, Edward
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: VOTE:SUPPORT

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
   ___ yes ___no
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
   ___yes ____no
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.
   ___yes ____ no

I am sending this email to the non-SUPPORT subcommittee members for input as the SUPPORT SUBCOMMITTEE has already voted.
Please respond by November 25
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT AUTHORSHIP
Date: Tuesday, November 24, 2009 9:44:00 AM

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, November 24, 2009 9:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

Hi Rose- that sounds great.....Nancy

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 1:04 PM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From:	Higgins, Rosemary (NIH/NICHD) [E]
To:	"Cunningham, Meg"; "[SCRN] Stoll, Barbara"; "alaptook@WIHRI.org"; "Bell, Edward"; "bpoindex@iupui.edu"; "Das, Abhik"; "goldb008@mc.duke.edu"; "jfrantz@tuftsmedicalcenter.org"; "Kathleen.A.Kennedy@uth.tmc.edu"; "kurt.schibler@cchmc.org"; "kwatterberg@salud.unm.edu"; "mcw3@cwru.edu"; "mcaplan@northshore.org"; "Pablo.Sanchez@UTSouthwestern.edu"; "richard.ehrenkranz@yale.edu"; "Roger.Faix@hsc.utah.edu"; "sshankar@med.wayne.edu"; "vanmeurs@leland.stanford.edu"; "Wally Carlo, M.D."; "jon.e.tyson@uth.tmc.edu"; "Michael Cotten"; "Wallace, Dennis"
Cc:	"jwaidne@emory.edu"; "Brenda Vecchio"; "gonza025@mc.duke.edu"; "Nancy.M.Smith@uth.tmc.edu"; "lmoore@med.wayne.edu"; "Zaterka-Baxter, Kristin"; "Huitema, Carolyn Petrie"; "Irene, Amanda"; "Newman, Jamie"; "Auman, Jeanette O."; "Pickett, James"; Archer, Stephanie (NIH/NICHD) [E]
Subject:	RE: Steering Committee Call Tuesday
Date:	Tuesday, November 24, 2009 9:14:00 AM
Attachments:	Evans comprehensive proposal for protocol review committee1 (2).docx Summary review 24Nov0909.doc

Hi
Attached is the comprehensive care proposal and yesterday's Protocol review summary (This will be posted on the RTI private site) for discussion.

Recent vote results:
Allow Matt Laughon and Ron Goldberg to use NRN GDB and Benchmarking abstract information in a CHOICE grant – approved 13 yes votes.

NRN Authorship on papers (author order by site) – We will leave the current policy in place – votes were:
Leave "as is" – 10
Change to absolute number recruited – 5
New combination – 3 with proposals for:

- 75% credit for absolute numbers and 25% for enrolled/eligible
- 33% for absolute #, 33% for % enrolled of screened and 33% of % enrolled of eligible
- Two tiers, with centers whose total enrollment is below some threshold going to the second tier. The threshold might be based on the fraction of total enrolled such as N/no of centers participating. IE for support 1300/20=65

For the SUPPORT manuscripts, there are three requests for authorship which have been approved by the SUPPORT Subcommittee:

1. For Alabama, Ambal is requested to be an author based on his pivotal role in the trial at the highest recruiting site.
2. For Rochester, Dale Phelps is recommended to be added to the oximetry paper due her role in training for ROP and source of ROP advice during the trial.
3. For Cincinnati, Ed Donovan is recommended to be added to the CPAP paper for his role in trial training and serving on the subcommittee until Kurt took over in 2006.

I will send a vote to the SC members for the above three items.

Thanks
Rose

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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, November 24, 2009 8:33 AM
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; Wallace, Dennis
Cc: jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; lmoore@med.wayne.edu; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; Newman, Jamie; Auman, Jeanette O.; Pickett, James
Subject: RE: Steering Committee Call Tuesday

Reminder for today's call.

From: Cunningham, Meg
Sent: Friday, November 20, 2009 11:04 AM
To: [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; ifrantz@tuftsmedicalcenter.org; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mcw3@cwru.edu; Mickey Caplan (mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; 'jon.e.tyson@uth.tmc.edu'; 'Michael Cotten'; Wallace, Dennis
Cc: 'jwaidne@emory.edu'; 'Brenda Vecchio'; 'gonza025@mc.duke.edu'; 'Michelle Smith (Nancy.M.Smith@uth.tmc.edu)'; 'lmoore@med.wayne.edu'; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; Newman, Jamie; Auman, Jeanette O.; Pickett, James
Subject: Steering Committee Call Tuesday

Dear All -

The next standing Steering Committee call is scheduled for Tuesday, November 24th at 3 PM ET.

Please Dial:
Outside the USA 1-203-310(b) (6)
or Within the USA 866-675(b) (6)
Then, enter Participant Passcode: (b) (6) #

Steering Committee Conference Call Agenda 11/24/2009

1. Comprehensive Follow-up Care Update
2. Status of SUPPORT Papers – pending final versions
3. INS Update
4. NEST Update
5. New business

Thanks!
Meg
Meg Cunningham
RTI International
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Washington, DC 20005
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Comprehensive Follow-Up Care of High-Risk Infants

A T3 Comparative Effectiveness Study

Jon Tyson, MD, MPH
Patricia W. Evans, MD
Roy Heyne, MD
Claudia Pedroza, PhD
Luisa Franzini, PhD
All PIs and Follow-Up PIs
Of the NICHD Neonatal Network

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Purpose, Scope, & Anticipated Contribution. We propose a multicenter, comparative effectiveness trial among high risk infants discharged from a neonatal ICU to demonstrate that their incidence of serious illness—illness resulting in death, admission to a pediatric ICU (**PICU**), or prolonged hospital stay—is lower with comprehensive then conventional follow-up (**FU**) care. We previously conducted a large single-center randomized trial funded by the Agency for Health Care Policy and Research and published in JAMA[1]) which showed that comprehensive FU care substantially reduced life threatening illness (death or PICU admission) without increasing health care costs. While these findings have not been questioned, few centers provide such care. The study we now propose is to address the obstacles, establish comprehensive care, and verify the benefits in multiple centers of the NICHD Neonatal Research Network (**NRN**). This study clearly fits the NRN mission to conduct clinical trials and outcomes research to augment the short & long term outcomes of high risk infants. It also fits well with multiple priorities for comparative effectiveness research that have published by the Agency for Health Care Quality and Research and the Institute of Medicine, particularly research: "to compare the effectiveness of... comprehensive support services for infants and their families following discharge from a neonatal intensive care unit." If the proposed research is successful, it would establish a new model of care for neonatal FU programs.

Acceleration of Scientific Research & Creation and Retention of Jobs. Operating under a competitive cooperative agreement, the NRN has been a quite successful in conducting comparative effectiveness studies to advance neonatal care. However, it has not yet undertaken a trial of FU care, and all NRN research funds for the coming 2-3 years have been committed. As described below, the proposed study would advance NRN research by addressing an important neglected topic in pediatrics--the care of high risk infants after discharge home. The study would also promote a neglected kind of pediatric research--T3 translational research, which is designed to successfully provide effective methods of care in different settings.[2,3,4] The study will help stimulate the economy by retaining/hiring clinic staff, research nurses, & nurse practitioners in multiple centers. If successful, it will also promote the long term goal of increasing health care access and effectiveness while controlling costs.

Rationale for Comprehensive FU Care. FU clinics—in marked contrast to neonatal ICUs—have changed little in the past 50 years. Yet, there has been a dramatic increase in the number of high risk infants who survive to be discharged home with a complex mix of ongoing problems, including chronic lung disease, neurologic, gastrointestinal, nutritional, and other problems. Few practicing pediatricians can commit the time or have the experience to develop and maintain skills in treating the acute and chronic illnesses and complications common among these infants. Caregivers with special availability, experience, and commitment are needed during the transition between NICU discharge and one year of age when these infants' problems are more readily treated by pediatricians in the community.

Evidence for Comprehensive Care. The trial noted above included 887 very low birth weight, ventilator treated infants discharged from Parkland Memorial Hospital (Dallas, TX) and randomly assigned to either a) conventional FU care (which in that center included care for chronic illnesses and usual well baby care) or b) comprehensive FU care (which *also* included care for acute illnesses from pediatrician-supervised practitioners and 24-hr access to the primary caregiver in the clinic or by phone). The infants were treated at Children's Medical Center, the private hospital adjacent to Parkland. Faculty supervised residents in the clinics and emergency rooms treated acute illnesses among conventional care infants. The primary outcome was life-threatening illness (illness resulting in death or PICU admission) before 1 year. Comprehensive care resulted in:

- 47% fewer infants with life-threatening illness (33 vs. 62; p=0.001).
- Comparable known deaths (11 vs. 13; p=0.68) but fewer infants who were not known to be alive at 1 year adjusted age despite yearly searches of local clinic and hospital records or Texas Medicaid records (9 vs. 28; p=0.001)
- 57% fewer PICU admissions (23 vs. 53, p=0.003)
- 42% fewer intensive care days (254 vs. 440, p=0.003)

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- 18% fewer emergency department (**ED**) visits (597 vs. 730; p <0.03)
- A mean increase of only 3.1 FU clinic visits and 6.7 phone calls per infant.
- No increase in mean total health care costs per infant to one year: $6265 for comprehensive care vs. $9913 for conventional care (p>0.05) (independently assessed from a societal perspective by health care economists at the U.T Houston School of Public Health using department-specific cost to charge ratios).
- No reduction in the hospital's financial "bottom line" (mean of reimbursements minus costs per infant = $1070 loss with comprehensive care vs. $2977 loss with conventional care.)

Though not formally assessed, costs to the Medical School were undoubtedly lower with comprehensive than conventional FU care due to the lower salaries for faculty in the clinic than in the PICU and lower total faculty hours devoted to treating these infants. Parental expenses and inconvenience were also clearly reduced. .

Thus, the findings of this large trial indicate that comprehensive FU care can have major benefits for high risk infants without increasing costs from a societal, hospital, medical school, or parental perspective.

Generalizability to other locales. The benefits of comprehensive care might be less in some places where the parents of high risk infants are better educated or their community pediatricians are unusually available and skilled in treating such infants. However, the Dallas trial may well provide a conservative estimate of the potential incremental benefits over conventional FU care in most locales because: a) conventional FU care in Dallas—in contrast to that in most centers--included care for chronic illnesses (a factor likely to have reduced the observed incremental benefit of comprehensive care); b) insurance coverage did not affect access to conventional FU care in the Dallas trial. In many locales access to private practitioners is limited for uninsured high risk infants. Even for those who are insured, access may be limited by inadequate reimbursement for all the time required to treat complex conditions or by the reluctance of the physician to see patients that he/she does not feel well trained to treat; c) immediate access to hospital facilities for infants presenting with life-threatening illnesses or complication is not available in the office of most private practitioners as it was for infants given conventional FU care in Dallas and in hospital-based FU clinics in other locales.

Ready access to care-givers with special availability, experience, and commitment has been found to be beneficial across a broad variety of high risk populations In the trial above, the number needed to treat (**NNT**) with comprehensive care to prevent one child with life-threatening illness was only 13. Even if the NNT were twice this value in other locales, it would still be an extraordinarily low for such an important benefit.

Need for a T3 Comparative Effectiveness Trial. Neither the results of the Dallas Trial nor the potential value of comprehensive FU care in other locales has been questioned by neonatologists or FU clinic directors. Yet, we know of only two U.S. cities where such care is available: Dallas, where the trial findings convinced the administration of Children's Medical Center, Parkland Memorial Hospital, and UT Southwestern to jointly fund the program (directed by Dr. Heyne), and Houston, where the Chairman of Pediatrics agreed to fund a program (recently started by Drs. Evans & Tyson).

The paucity of comprehensive care programs presumably reflects the current funding of medical care (with little financial incentive to reduce hospital admissions by improved outpatient care), the traditional goal and staffing of FU clinics (to assess neurodevelopmental outcome), and the need to tailor comprehensive care programs to the local setting. Such issues may be best addressed through T3 translational research, research to assess how to most successfully provide effective methods of care in different practice settings.[2,3,4] Such research often follows T2 research, such as the Dallas Phase III trial described above, that demonstrates the clinical effectiveness of health care interventions. (T2 research generally builds on T1 research, e.g., preclinical or Phase II/II trials) to develop efficacious interventions,).

We propose a T3 comparative effectiveness study in which each intervention center will initiate a comprehensive care program, develop methods to progressively increase its efficiency and effectiveness within the local setting. In an environment in which health care funding is increasingly geared to improve outcomes and control costs, such results from a high profile study would help promote adequate reimbursement and wide

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use of comprehensive FU care. With an already well established FU mechanism, the NRN is best positioned to conduct such a study most effectively and with lowest research costs.

Study Design & Hypotheses. Designs other than randomized trials may well be needed for comparative effectiveness research, particularly T3 studies.[5] We will assess outcome changes in successive infant cohorts as intervention centers introduce and refine comprehensive care in their particular setting. The cohorts will be based on date of discharge home, and the outcomes of each cohort will be assessed through one year postnatal age. During the 3 year study, we will assess infants discharged from intervention centers during two successive 6-month pre-intervention control periods and three 6-month intervention periods in intervention centers. (The inclusion of two 6-month control periods will allow each intervention cohort to be compared to a cohort discharged one year earlier and will facilitate adjustment for season in the analyses.) We will also assess infant cohorts born during the same time periods in comparison centers that do not provide comprehensive care.

Study population: Intervention centers can choose provide comprehensive care to not only infants born at <26 completed weeks, a group that is assessed as part of Network follow-up program, but also other predefined high risk groups of infants (e.g., all infants <29 weeks gestation). The target population will be limited to infants living within specified geographic boundaries to exclude infants for whom comprehensive follow-up care could not be reasonably provided by center staff. Comparison centers are not expected to assess infants who would not be evaluated in the Network follow-up program. (The differences in population of intervention and comparison centers will be addressed as described below in the hypotheses and analyses sections.) Seven or eight NRN centers will be selected to serve as intervention centers, based on their capacity and commitment to meet the requirements for comprehensive care described below. UT-Houston which only recently began implementing comprehensive care will be considered an intervention site; UT-Southwestern in Dallas has a well established comprehensive primary care program and will not be included as either intervention or comparison center.

Primary hypotheses: **1. In analyses controlling for center, serious illness--death, PICU admission, or prolonged hospital stay (>80th percentile for all study infants) between discharge from a neonatal ICU and before 12 months after birth--will be progressively reduced among successive cohorts of eligible high risk infants in the intervention centers; 2. The reduction in serious illness between discharge from a neonatal ICU and one year age among infants followed in all NRN centers (infants ≤26 weeks gestational age) will be greater in intervention centers than in comparison centers that do not implement such care.**

The primary outcome includes a prolonged hospital stay (which was not included in the primary outcome in the Dallas trial) to afford greater statistical power and to capture additional expensive and medically important hospitalizations that would not be identified by PICU admissions only.

Secondary hypotheses (addressing secondary outcomes assessed in comparisons within intervention centers and between intervention and comparison centers): 1) Comprehensive care will decrease total PICU days; 2) The reduction in serious illness with comprehensive care will be greatest for infants of poorly educated mothers; 3) Comprehensive will increase maternal satisfaction; in intervention centers; 4) Comprehensive care will not increase total care costs as shown by a formal economic evaluation in two Network centers (UT Houston and another yet to be named).

Tertiary Hypothesis (addressing process measures collected only in intervention centers): Assessment of successive infant cohorts will indicate a successively 1) greater % of eligible infants who enroll in the comprehensive care program, 2) greater % of eligible infants who continue in the program through one year of age; 3) a lower number of ED visits expressed as a % of all visits; 4) a lower % of infants who are admitted to hospital without having been previously seen and/or discussed by phone with comprehensive care personnel.

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Requirements for comprehensive FU care. Intervention centers will differ somewhat in the services provided and how they are provided in their locale. However, all will meet the following criteria: 1) Staff: Small team of caregivers (physicians +/- pediatric nurse practitioners or physician assistants) highly committed to improving the care of high-risk infants 2) Clinic services: Care for chronic and for acute illnesses (goal: same day) as well as well-child care (immunizations, neurodevelopmental assessment, & anticipatory guidance); 3) Staff availability. Caregivers will be available to provide care in person 8 hr/d for 5 d/wk. Families will have pager access at all hrs to a team member, routinely a primary care provider. When an infant is referred to the ED, the ED physician will be called to discuss the infant's problems and management. Comprehensive care will be provided until at least one year postnatal age.

Support to establish comprehensive FU care. Support to help assure the feasibility of this demanding study will include $1250 capitation per study infant given comprehensive care and $300 capitation per study infant not given comprehensive care. The budget (see below) also includes some start up costs, support for the physician project director at each comprehensive care center and support for training and annual meetings. Clinical services provided to comprehensive care patients will also be billable. As for other NRN studies, support will also be needed from the hospital, Department, or Division. This support can be fostered by the Dallas cost-effectiveness data and by local needs and expected changes in health care funding. In helping to promote such support, we provided a series of questions for discussion by hospital administrators and Department Chairs. (Examples include: Are your PICU beds often full? Do the reimbursements fail to meet the true cost of care for Medicaid infants? Do you expect reduced reimbursements for PICU care or higher reimbursements for outpatient preventive care? Do you want to reduce ED visits? Are you having difficulty recruiting intensivists? What additional effort and expense is required to recruit and support intensivists than FU clinic personnel? Are there faculty who would want to be involved in this research? Would malpractice risks be reduced by FU clinic that addresses increases augments care, parental concerns and increases their satisfaction? Would a model FU program attract strong community recognition [as in Dallas]?)

As noted below, FU staff will receive support and advice in periodic visits and phone calls from Dr. Heyne who directs a well established program (Dallas) and Dr Evens who recently initiated a program (Houston). To help optimize the care of the infants and promote the career development of FU faculty, Drs. Tyson, Evans, and Heyne would coordinate efforts among NRN FU PIs to conduct systematic reviews of outpatient methods of treating problems common in high risk infants, develop practice guidelines based on best current evidence, and define a research agenda to address important unanswered questions in NRN observational studies or trials. We also expect multiple publications describing and relating the process and outcome measures in this T3 study

Study Phases: As described below, five infant cohorts discharged in successive 6 mo periods will be studied:

- 2/01/10 – 7/31/10: Control Cohort 1 (f/u to ~4/3o/11)
- 8/01/10 – 1/31/11: Control Cohort 2 (f/u to~10/31/11)
- 2/01/11 – 7/31/11: Intervention Cohort 1 (f/u to ~4/3o/12)
- 8/01/11 – 1/31/12: Intervention Cohort 2 (f/u to ~10/31/12)
- 2/01/12 – 7/31/12: Intervention Cohort 3 (f/u to ~4/30/13) allowing 3 months for completion of analyses, submission of the primary manuscript, and initiation of the dissemination plan before completing the funding period (8/30/13).

The study will be conducted as follows:

Before 8/1/10 (anticipated start of funding). Completion within 3 yrs of funding will be feasible because of extensive prior planning and the Network resources and research infrastructure. The concept proposal has been approved by the NRN and discussed in depth at 3 meetings and by phone with individual PIs and Follow-Up PIs. Further discussion and planning will occur during visits by Drs. Evans &/or Heyne to the 7-8 intervention centers. To help assure that all important issues have been carefully considered in planning the study, we will

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have prepared a draft of the introduction and methods section and a skeleton of the tables for the final manuscript for the study.) Prospective data collection will begin for **Control Cohort 1,** control infants meeting exactly the same criteria as infants targeted for comprehensive care in the same center and discharged on or after 8/1/09-1/31/10.

8/01/10 – 1/31/11**:** Preparation phase with personnel hiring and training for comprehensive care in intervention sites. All sites will initiate data collection for **Control Cohort 2** (control infants) discharged during this time and continue data collection for Cohort 1.

02/01/11 -7/31/11 Initiation of comprehensive care; enrollment of **Intervention Cohort 1** (study infants discharged during this period); data collection to be completed for Control Cohort 1 and continued for Control Cohort 2.

8/01/11 – 1/31/12: Enrollment of **Intervention Cohort 2** (study infants discharged during this period). Data collection will be completed for Control Cohort 2 and continued for Intervention Cohort 1.

2/01/12 – 7/31/12: Enrollment of **Intervention Cohort 3** (study infants discharged during this period). Data collection will be completed for Intervention Cohort 1 and continued for Intervention Cohort 2.

8/01/12 – 1/31/13 Data collection will be completed for Intervention Cohort 2 and largely completed for Intervention Cohort 3. Audits and data cleaning will be completed for all collected data.

1/31/13-7/31/13 Depending on when the last infant reaches 12 months age, data collection will be completed for all cohorts by ~ 4/30/13. Audits, data cleaning, data lock, and data tables will then be quickly completed. As for other Network studies in which Dr. Tyson was responsible for preparing the primary manuscript, it would be promptly prepared (building on the draft of the introduction, methods, and data table skeletons prepared before initiating the study) and ready for internal review by no later than 7/1/13 and submission for publication within 1-2 months.. Dissemination of results would begin as soon as the final analyses were completed and would be well underway by the end of the funding period 8/31/09.

Outcome and Process Measures. The proposed research has been designed to assure collection of important outcome and process measures while minimizing the time, effort, and expense required for data collection.

- All sites: For all eligible infants as described above, data collection would include data items included in the Network generic data base, maternal education at discharge, and the following data items between hospital discharge and one year age: death, PICU admission, PICU days, hospital admission, and total hospital days to 12 months age. (Hospital admissions will be identified by local records, maternal report and Medicaid records [with consent to access these records obtained at enrollment to the study]).
- Intervention sites will also collect
    - Percent of infants in each cohort who enroll in comprehensive care during each intervention period and percentage who continue in the program through one year of age
    - Percent of infants lost to follow-up at one year of age
    - Number of ED Visits
    - Visits/phone calls
    - Maternal satisfaction with care after NICU discharge, using an adaptation of the CAHPS Clinician and Group Survey Child Primary Care Questionnaire" from AHRQ.
- Three selected intervention sites, including UT Houston:
    - Detailed economic data concerning cost of all inpatient care and of comprehensive vs. routine follow-up program outpatient care as specified by the involved health care economist (Luisa Franzini, PhD, UT Houston School of Public Health).

Statistical Analyses. The analyses will be performed by Research Triangle International. To test Hypothesis 1 that severe illness will be progressively reduced in intervention centers, hierarchical analyses will be performed using data from all high risk infants intended to receive comprehensive care (whether or not they received it) among intervention centers. The dependent (outcome) variable will be serious illness, and the independent (predictor) variables will be time period, season at discharge, center, maternal education, and other important

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social and medical variables at discharge predictive of severe illness. (To assure unbiased analyses, these variables will be selected based on univariate models and clinical judgment before performing the logistic regression analyses). A progressive reduction in serious illness would be identified by a negative slope when relating risk adjusted incidence of serious illness to period. To test Hypothesis 2, multi-level analyses will be performed using all infants from intervention and control sites who qualify for generic follow-up (see above). The dependent variable will be serious illness and the independent variables will be patient outcomes will be group (comprehensive care or comparison), period, maternal education, medical variables at discharge predictive of serious illness (selected as above). Hierarchical logistic analyses will assess group effect after controlling for individual and center level covariates.

In accordance with recent recommendations for clinical trials,[6] Bayesian as well as frequentist analyses will be conducted by Dr. Pedroza (who conducted the analyses for a recent NRN publication in the New England Journal of Medicine.[7] Prior probability and 95% credible intervals will be based on values elicited from the Network PIs and FU PIs provided relevant literature.

Sample Size and Interpretation of Results: We expect intervention centers to provide comprehensive care to approximately twice the number of infants they would see for generic NRN follow-up. (Based on follow-up data for infants ≤26 wks GA born in 2006 and the Network generic neonatal data for the number of survivors <29 wks GA, this could be achieved simply by following infants 27-28 weeks, if not also high risk infants born at a later GA who developed specified complications.) If so, the number of patients given comprehensive care in the proposed study is expected to equal or exceed that in the large Dallas trial. With the control cohorts in both the intervention centers and the control centers, the number of infants given usual care will be approximately two fold that in the Dallas trial. However, in a 3 year study, the power for frequentist analyses will be limited by the number of infants who can be enrolled and the need to control for center differences. For this reason, it is possible that there will be no statistically significant reduction in serious illness, particularly for the second primary hypothesis that would be tested only in infants ≤26 weeks gestation. However, we expect that Bayesian analyses would support the benefit of comprehensive care. As long as there is no evidence that serious illness is increased by comprehensive care, the study findings could justify recommending comprehensive care as a method that increases access to care, provides a medical home during a period when high risk infants are especially prone to serious illness, decreases loss to follow-up, and augments parental satisfaction without increasing cost.

Budget. CHOICE grant funding for this project will be requested from AHRQ, including:

1) Capitation: approximately $750,000, depending on sample size:
    a. $1,250 per comprehensive care intervention subject to cover research related costs and some training, incremental personnel, and other implementation costs.
    b. $300 per control subject at intervention and control centers to cover research costs including data collection and reporting
2) Non-capitation; Approximately $2,500,000 to cover
    a. PI (Tyson) + 2CoPI (Heyne and Evans) support (25% for the PI as required by the RFA and 20% for the CoPIs)
    b. Physician Project Director costs for 7-8 intervention centers (15% each)
    c. Provider training not covered by capitation
    d. Incremental clinic costs for providing comprehensive care
    e. Economist (33%), Luisa Franzini)
    f. Data entry
    g. Dissemination costs

RTI costs are yet to be determined.

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Estimated total project cost: $3,250,000 excluding RTI costs and indirect costs. The grant can cover costs incurred during the 90 days prior to the start of the funding period.

REFERENCES

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[3] Naik AD, Peterson LA. The neglected purpose of comparative-effectiveness research. N Engl J Med 2009; 360:1929-31.
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[5] Congress of the United States Congressional Budget Office. A CBO paper. Research on the comparative effectiveness of medical treatments, December 2007,
[6] Wijeysundera DN, Austin PC, Huex JE, et al. Bayesian statistical inference enhances the interpretation of contemporary randomized trials. J Clin Epidemiol 2009; 62: 31-21, e5.
[7] Morris BH, Oh W, Tyson JE, et al. Aggressive vs, conservative phototherapy for infants with extremely low birth weight. N Engl J Med 2008l 359: 1885-96 (see appendix).

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DATE: November 24, 2009

TO: Jon Tyson, MD, Patricia W. Evans, MD, Roy Heyne, MD, Claudia Pedroza, PhD, and Luisa Franzini,PhD

FROM: Richard A. Ehrenkranz, MD
Chair, Protocol Review Subcommittee

RE: Comprehensive Follow-Up Care of High-Risk Infants – A T3
Comparative Effectiveness Study

The Protocol Review Subcommittee reviewed this protocol during its conference call on November 23, 2009. Written comments were provided by Brenda Poindexter, Michael Acarregui, Abhik Das, Jim Zhang, and Rose Higgins; those comments are attached to this summary.

As you will appreciate from the reviewers' comments below and from Rose's brief email following the conference call, the Protocol Review Subcommittee considered many issues related to the design and feasibility of this proposal, including:

1. The proposal lists "5 infant cohorts discharged in successive 6 month periods" beginning 2/01/10-7/31/10. However, since the earliest date for the start of AHRQ funding would be September 2010, and since most intervention centers and RTI will not be able to initiate study related activities until funding is provided, the study's timeline should be revised and made consistent with the AHRQ timeline.

2. Consider including a table in the application that lists the current "primary care" practices provided by the likely intervention centers and the care elements that would be added as part of the comprehensive follow-up care initiative.

3. Specify a clear definition of the infants eligible to receive comprehensive follow-up care in intervention centers. As written, this aspect of the application is too vague and would permit each intervention center to define its potential population. While that strategy might be the best "real world" approach (and eventually how this concept might be generalized), it will make interpretation of the study's results quite difficult. It is also important to note that the data system for non-GDB study infants will be built upon the current system and that a new data system will not be designed.

4. It appears that the intervention centers have been self-selected. Therefore, the comparison, ie control, centers may differ markedly from the intervention centers, for example due to the involvement and/or availability of developmental pediatricians, pulmonologists, and private pediatricians which diminishes the need for a comprehensive follow-up care program. Furthermore, the existence of such center-specific characteristics may prevent an otherwise interested center from choosing to be an intervention center. As you are probably aware, there is a lot of potential for selection bias in the current study design. Therefore, the method in which centers will be selected to be intervention or comparison centers should be clarified.

Normally, the Protocol Review Subcommittee would request that a revised protocol be submitted to the Subcommittee before recommending that it be considered by the Steering Committee. However, given the AHRQ submission deadline of December 16, 2009, the limited time available for the investigators to revise this proposal, and the Subcommittee's level enthusiasm if this study

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were funded by AHRQ, the Subcommittee recommends that it be considered during the monthly Steering Committee conference call on November 24, 2009. Furthermore, the Subcommittee recommends that a letter stating that the NRN infrastructure may be used in the performance of the comprehensive follow-up care study, if it is funded by AHRQ, accompany the application. We hope that the comments contained in this summary review will be helpful in your efforts to revise the application.

Comments submitted by Brenda Poindexter:

The proposal is for a comparative effectiveness trial of a comprehensive follow-up care program versus standard care of extremely premature infants. The primary hypothesis is that comprehensive care will reduce serious illness (defined as death, PICU admission, or prolonged hospital stay) between discharge from a NICU and before 12 months after birth.

The rationale for this proposal is compelling given the results of the previously published study conducted in Dallas. However, as the investigators point out, it is not clear how generalizable the results of the Dallas study will be to other locales.

The study design is unique in that outcomes will be assessed in successive infant cohorts, providing intervention centers the opportunity to not only introduce, but also refine comprehensive care in their particular setting. Infants discharged from the intervention center will be assessed in 6-month periods – the first two periods will be pre-intervention control periods followed by three intervention periods. Infants at comparison centers that do not provide comprehensive care will similarly be assessed in the same five 6-month periods of time.

Overall, I am enthusiastic about this protocol and think that the rationale and evidence for comprehensive care is strong. The majority of my comments relate to implementation of comprehensive care. If the investigators are able to secure funding outside of the Network with a CHOICE grant from the AHRQ, I would support the proposal moving forward.

COMMENTS:

1. Study Population: The protocol states that centers can choose to provide comprehensive care not only to infants born at <26 weeks gestation, but also to other predefined high risk groups of infants – given the complexity of introducing and refining a new paradigm of care, it would seem that all centers should begin with the same focused group of eligible infants (those <26 weeks) for at least the first intervention period; once the comprehensive care model is well-established, other high-risk groups of infants could then be added depending on availability of funding to do so. Also need to better define the geographic boundaries for eligible infants.
2. Informed Consent: When would consent be obtained for the protocol? Given the prospective data being collected, I would surmise that most IRBs would require consent. I would be interested to hear the investigators thoughts on this.
3. Subspecialty care: In the model of comprehensive care, how are consulting subspecialists integrated into the model? For example, at many centers, the developmental pediatricians (same individuals who staff the follow-up visit at 18 months) are already seeing these high-risk babies for transition to oral feeds as early as 2-4 weeks following NICU discharge. In addition, many infants with BPD are followed by Pediatric Pulmonologists if they go home on oxygen. Would the intent be for the comprehensive care pediatrician to take the place of these subspecialists or rather to coordinate care and provide a "medical home"?

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4. Comparison centers: Much of the information needed to assess outcomes will be difficult to obtain from infants who are not being seen in the comprehensive care model (those at control centers and those at intervention centers in the first two control cohorts). I would assume that many of the centers have more than one ED where these infants might go for urgent care. How do the investigators propose that infants in the comparison cohorts (both at comparison centers and during the first two cycles at intervention centers) be tracked?
5. Role of teaching residents: I assume that all of the participating Network centers have resident clinics that are currently the primary care providers for many of these high-risk infants. How could residents potentially be integrated into the comprehensive care model?

Comments submitted by Michael Acarregui:

The current proposal is a multicenter, comparative effectiveness trial of comprehensive versus traditional follow up of NICU graduates of <27 weeks gestation with an option to enroll and include infants < 29 weeks. The primary outcomes are illness resulting in death, PICU admission and prolonged hospital stay through one-year postnatal age. In addition to the two lead centers (Dallas and Houston) 7-8 intervention centers will enroll infants into a comprehensive care follow up program that includes the provision of all primary care (8 h, 5 days per week) plus 24 h, 7 day per week on call availability of a care provider who can take a call and make referral to a local ER if needed. The study will progress with the enrollment and follow up of 5 successive 6-month cohorts including the initial two control cohorts. Concurrent control patients will also be followed at intervention and other NRN centers. Funding will be provided by capitation of enrolled patients and to fund Project Director costs at intervention centers, training costs and incremental clinic costs.

Comments

1. A successive design is proposed in order to account for changes that will occur in care provided by intervention centers as they refine their center approaches to comprehensive care. What is not clear is how this design will affect the numbers needed to enroll. This will depend on the comparisons to be made in the data analysis. Will the three intervention cohorts be evaluated as a single group or will each cohort be analyzed separately? If separately, will more patients be needed in the early cohorts as there may not be as much difference in the outcomes between intervention and control patients since the comprehensive care may not be fully refined? If analyzed as a combined cohort, then is it necessary to even study successive cohorts? Additionally, the use of two initial cohorts as controls will result in an historical cohort for comparison. This may not be the most useful comparison as the care of those not in the comprehensive care cohort at intervention centers may benefit from the increase in care infrastructure that will be inevitable as a result of participation as an intervention center.

2. The protocol initially states that the enrollment of infants >26 weeks will be optional but later indicates that the number to enroll should be twice the number of infants under 27 weeks. These numbers will only be achieved by enrolling infants under 29 weeks. Therefore, enrollment of infants < 29 weeks should be a study requirement. This is important not only to increase study numbers but to recognize that these infants are also extremely vulnerable to illness and at risk for rehospitalization. If the study results are to be generalizable to an "at risk" population then it is important to not just include those at greatest risk (<27 weeks).

3. If infants outside the GDB are to be enrolled, can outborn patients be included?

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4. Outcome Measures are appropriate. I do wonder if it would be important to compare growth parameters age 18-22 months for the GDB patients as a potential indicator of efficacy of comprehensive care as it could also be hypothesized that closer follow up with individuals focused on the needs of ELBW patients will see that the nutritional care is optimized in these patients.

5. Will it be permissible to refer to any ED or only the center ED at times when the clinic is not open?

6. When will patients be enrolled in the study? Perhaps best to approach a month or so prior to anticipated discharge so that other arrangements for post discharge care have not already been made at the time that patients are approached for informed consent for this study.

7. Analysis of the data should also be stratified by gestational cohorts <27 weeks and 27-28 weeks as the greater gestational age cohort will likely have more time in follow up (average discharge at an earlier postmenstrual age) than the earlier gestational age cohort that will likely be discharged at a later postmenstrual age.

8. The proposed budget includes items for capitation and non-capitation. The amounts proposed under capitation seem appropriate but may change significantly as sample size calculations are performed. The cost items that are to be covered by this capitation should be better delineated. For the non-capitation items the need for the approximate figure of $2.5 million is less clear as PI and Project Director support will amount to about 1.85 fte or about $450,000 in direct costs. I assume that item "d. Incremental clinic cost..." will include salary support for nurse practitioner or other provider support. This needs to be clarified in the application. Will participating centers submit individual requests for funding their specific study needs?

Overall, this is an interested and much needed study. Given the NRN infrastructure for follow up the study should be feasible. The greatest challenge is to make it relevant to the many that care for these infants and to policy makers. The demonstration of efficacy is in no way adequate to assure adoption of the therapy or approach to care. It will be important to delineate just what it is that makes these follow up clinics "special" and "expert" in the care of this patient population. If general pediatricians are providing this care with the assistance of multiple sub specialists, then how is that different from having a general pediatrician in the community manage the patients in the same manner?

Comments submitted by Abhik Das:

A T3 design seeks to assess how to most successfully provide effective methods of care in different practice settings. These studies are primarily meant to test what *system approaches/changes* are most effective at increasing the delivery of a new and proven intervention to the right patients at the right time, and then disseminate effective strategies. I don't see the stated primary hypotheses doing that. They are more traditional T2 hypotheses concerned with efficacy.

The 1st hypothesis is a before/after design [what has also been called a Non Equivalent Control Group (NECG) design], but there is no discussion of the biases (such as any other changes over time that may impact outcomes) that may entail. It is not clear why we need the study entrants divided into so many cohorts (two for control and three for intervention), and why control cohort(s) are enrolled before the intervention cohort(s). It seems like here we have clustering of patient

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within time period. Do we assume there are correlations among patients within the same time period? We also need indicator for whether the time period is in the control or intervention period. What center characteristics do we need to adjust for, because this will be very critical? Do we need to collect specific center level data for this purpose? More details laid out in the analysis plan (preferably in terms of regression equations) would be helpful in understanding exactly what is planned.

A rigorous and unbiased test of the 2nd hypothesis is difficult without a cluster randomized design where sites would be randomized to comprehensive care or usual care. If that is not feasible, NECG designs (sometimes also called quasi randomized designs) usually take great care to match sites in some way before assigning selected ones to the intervention. (There is a whole body of literature on NECG and quasi experimental designs that can be profitably explored for better designing this study.) The proposal mentions that center will be controlled in the analysis. This can't be done in the conventional manner with this design since the centers are embedded within the treatment groups, unless this refers to adjusting for a cluster effect.
With respect to the proposed Bayesian analysis, prior elicitation is complex and we need more details here. Using a non-informative prior alongside is also recommended. In this connection, the stated expectation that Bayesian analysis will show a benefit for comprehensive care needs to be quantified.

The proposal says that the analysis will be done at RTI but also says Dr. Pedroza will do "Bayesian as well as frequentist analysis". I am not sure how that is going to work. We need a clear understanding of this beforehand both to convince reviewers at AHRQ of the merit of this application (some reviewers may find statisticians at both institutions as duplicative), and to avoid misunderstanding later on.

The sample size discussion is weak. Doing a parallel Bayesian analysis does not absolve the need to have sufficient sample size to provide credible results. At a minimum, there has to be some notion of expected effect size and power available given the expected sample size for both the primary outcomes, so that the NRN has some idea of the probability of this study generating usable results. We also need these numbers to establish credible enrollment time lines. Specifically, the following issues need addressing:

First, there is little information on the exact number of hospitals that will be included in the study. There is no discussion of how these centers will be selected. The suggestion that six or seven intervention centers would need to be identified, recruited, and receive training prior to the beginning of data collection in 02/2010 is a strong and unsupported assumption. This problem is further complicated by the suggestion of comparison centers with no mention of their potential number or the criteria for their inclusion. Would comparison sites truly be comparable to intervention sites? One would assume that intervention sites would be chosen for a number of logistical factors including their willingness to host a NRN comprehensive follow up care unit.

Second, there is no estimate of the number of infants receiving comprehensive and standard follow up care. The sample size section offers that intervention centers would provide comprehensive care to approximately twice as many infants as they would for a generic NRN follow up. Is this a realistic assumption? This concern is amplified by the lack of specificity regarding location of intervention and comparison centers. Additional concerns involve the ability of the intervention centers to provide comprehensive care (or not provide comprehensive care) on a case by case basis. This stands as a serious threat to the conclusion validity of the study. One could easy anticipate well intentioned practitioners steering comprehensive follow up to those

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infants they judge will benefit the most from additional services rendering comparisons non-equivalent.

Third, there is no discussion of the impact of clustering on sample size. Even if we are able to recruit large numbers of participants in each center, the statistical power for a clustered design is based on the number of clusters, not the number of individuals, observed. The design includes around 8 centers in each arm of the trail, with five cohorts in each center. Have these implications been considered in planning the trial?

Comments submitted by Jim Zhang (NICHD Epidemiologist):

It is an interesting and potentially important study. From a study design perspective, I have the following questions and comments for consideration:

- Will the investigators use one-sided or two-sided statistical test for their main hypothesis?
- The investigators intend to employ two types of controls: internal and external controls.
- For internal controls: Will there be a period of overlap between conventional FU (controls) and comprehensive FU (intervention)? If the same team of researchers conduct both conventional and comprehensive FU at the same time, would "contamination" of intervention be a concern in this particular study?
- For external controls: Are the investigators able to show if the intervention and control centers are compatible in terms of baseline characteristics of the hospital and newborns using existing database data?
- One would assume that an intent-to-treat analysis will be used. Participation rate (receive the treatment) and retention rate (stay in the program to completion) may become an important issue for such an analysis. Could the investigators make any assumptions based on their previous experience?
- The statistical power and sample size calculation may be affected by several sources of complications: a) hospital clustering of the treatment (equivalent to a cluster randomization); b) participation and retention rates; c) potential protocol variation among the centers.
- In the analysis, it would be more advisable to use the two types of controls separately rather than to mix them together.

Comments submitted by Rose Higgins (sent to Jon before the call, who participated at the beginning of the call):

I have a couple of budget questions in advance of this afternoon's call - Do you have a line item for indirect costs?
The protocol states $1250 for each infant with comprehensive care, but the spreadsheet says $1500. I assume you want the 1500, correct?

Do you have a budget for the RTI costs to include coordinator time, programmers, statistician and PI?? (+indirects) Is it the line item marked b. RTI: Data Mgt., Stat Analyses, Prog.Admin?

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For the travel, I assume the 3 meetings for the 13 individuals are training and updating, correct? We have used $2000 per travel/training meeting due to increased airline costs.

Also, it is my understanding that protocol review (and ultimately the steering committee) would agree to the following as part of the AHRQ application:

The NRN supports this application and can provide the following:
Data Management system for GDB and FU as per the NRN GDB and FU studies. Additional data and data management to support this study are needed.

Current infrastructure at sites and data coordinating center provides a platform for which additional projects can be performed pending availability of additional funding to support these costs

You can either respond by email or join the call at 4 PM ET (866-675-3256 with pass code 560152#) to answer the questions.

Also - minor points -
Can we say "parental" satisfaction instead of "maternal satisfaction?"
For the infants < 29 weeks but > 26 weeks, how much information will be collected? Will the tracking and collection of information occur at the same time?
Can you develop a flow diagram of the control and intervention cohorts?

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 4:14:00 PM

We added Dale
But you are correct – I will send an email to the SC (I think I did for Dale)

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Monday, November 23, 2009 4:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

This is how the policy reads now for Primary Studies:

More than one author from a participating center
A second author from a participating Center, who has special expertise and/or contributes significantly to the development of a protocol, may be nominated by the Principal Investigator of that site. This second author must be approved by the study subcommittee and the Steering Committee. If the Steering Committee approves the inclusion of two authors from the same Center, the Center Principal Investigator will decide who will be listed as the first author from that center. If the second author nomination is rejected by the Steering Committee, the Principal Investigator of that site will determine the single author from the site.

Should it be changed?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, November 23, 2009 3:59 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

Subcommittee makes the decision on this one

Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Monday, November 23, 2009 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

It needs to go through the SC too.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, November 23, 2009 3:51 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT AUTHORSHIP

Add Ambal to the authorship list. Put him in right after the subcommittee members

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From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Monday, November 23, 2009 3:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Roger Faix; Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

Absolutely.

Brad

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 11:04 AM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Bradley Yoder; Roger Faix; Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Archer, Stephanie (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 4:13:49 PM

---

8 out of 8 yeses.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, November 23, 2009 4:13 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT AUTHORSHIP

From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Monday, November 23, 2009 4:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT AUTHORSHIP

Absolutely yes. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 1:04 PM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; Laptook, Abbot; Abhik Das (adas@rti.org); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Archer, Stephanie (NIH/NICHD) [E]
To: ""Wally Carlo"; "nfiner@ucsd.edu"
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Boilerplate | SUPPORT
Date: Monday, November 23, 2009 2:21:23 PM
Attachments: Boilerplate, Carlo, SUPPORT Oximetry, 2009-11-23.doc
Boilerplate, Finer, SUPPORT Ventilation, 2009-11-23.doc

Attached are the final boilerplate versions (with Ivan's last change in it). The last two pages include a table documenting that no authors reported any conflicts of interest for either paper.

Please let me know if you have any questions,

Stephanie

Stephanie Wilson Archer
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SUPPORT Oximetry (without FU)

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From: Finer, Neil <nfiner@ucsd.edu>
Sent: Monday, November 23, 2009 2:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Michele Walsh-Sukys; alaptook@WIHRI.org; Abhik Das; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Rich, Wade; nxs5 @case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT AUTHORSHIP

Importance: High

A big YES!!

On 11/23/09 10:04 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 1:53:12 PM

From: Walsh, Michele <Michele.Walsh@UHhospitals.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Nov 23 13:52:36 2009
Subject: RE: SUPPORT AUTHORSHIP

yes

Michele Walsh
beeper(b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 1:04 PM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

Hi
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Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

Visit us at www.UHhospitals.org.

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

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From: Michael O`Shea
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Marie Gantz
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF
Date: Monday, November 23, 2009 1:45:44 PM

Thanks Neil. Of course I defer to Abhik on the p value issue.

Mike

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 23, 2009 9:44 AM
To: Michael O`Shea
Cc: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Marie Gantz
Subject: Re: ++++CONFIDENTIAL: CPAP vs SURF

Thanks Mike
We will relook at these.
I think that we had nade a similar decision in previous iiterations and
then others wanted the p vales in Marie and Anhik - can we review?
Thanks

Sent from my iPhone

On Nov 23, 2009, at 4:18 AM, "Michael O`Shea" <moshea@wfubmc.edu> wrote:

> Neil,
>
> Congratulations on completing this trial - an amazing accomplishment.

> In the attached I offer a few editing suggestions.
>
> In Table 1, I would not include p values, as these are pre-
> randomization variables and the interpretation of a non-significant p
> value is that the difference between groups is not larger than can be
> explained by chance. But since we know that any differences are
> explained by chance (i.e., randomization), why do we need p values.
>
> In Table 2, I would not include p values, as any differences cannot be

> attributed to chance, as they are processes that were prescribed by
> the protocol with the intention of being different.
>
> In Table 3 I would round the p value to one significant digit.
>
> Thanks so much for your efforts.
>
> Mike
>
> _____
>
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Sat 11/14/2009 2:38 AM
> To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu';

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> 'sshankar@med.wayne.edu '; 'bsood@med.wayne.edu';
> 'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu ';
> (b) (6) ; 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org
> '; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu';
> 'edward.donovan@cchmc.org '; 'richard.ehrenkranz@yale.edu';
> 'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu ';
> 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org';
> 'Kathleen.A.Kennedy@uth.tmc.edu '; 'Jon.E.Tyson@uth.tmc.edu'; Michael
> O`Shea; 'mcaplan@northshore.org';
> 'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu
> '; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu';
'mgantz@rti.org '; 'ifrantz@tuftsmedicalcenter.org';
'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu ';
'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu';
'cotte010@mc.duke.edu '; 'goldb008@mc.duke.edu'
> Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org';
> 'mcunningham@rti.org '; 'petrie@rti.org'
> Subject: ++++CONFIDENTIAL: CPAP vs SURF
>
>
>
> Hi-
> Here is the most recent draft of the CPAP/surfactant paper.
>
> We will discuss on Monday's call.
>
> Thanks for all the assistance
>
>
> Rose
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD)
> [E]; Rich, Wade <wrich@ucsd.edu>
> Sent: Thu Nov 12 17:06:37 2009
> Subject: CPAP vs SURF
>
> Wally and Rose
> Here is the "final" CPAP vs Surf paper It fits NEJM and incorporates
> all suggestions although some were opposite so we made some choices.
> Please review
> Wally can you make sure our definitions for BPD etc are identical??
> Thanks
> I would like to get these submitted
> Please share with me your thoughts
> Be well
> Neil
>
>
> <SUPPORT NEJM Nov12 Final-oshea edits.doc>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 1:36:10 PM
Importance: High

From: Kurt Schibler <kurt.schibler@cchmc.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Nov 23 13:35:07 2009
Subject: Re: SUPPORT AUTHORSHIP

Hi Rose,
Yes, I am in favor of including Ambal as an author.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736(b) (6)
E-mail: kurt.schibler@cchmc.org

On 11/23/09 1:04 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi
> A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.
>
> Please send me a yes/no vote to include Ambal by 11/25
>
> Thanks
> Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 1:20:33 PM

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Sent: Mon Nov 23 13:19:59 2009
Subject: RE: SUPPORT AUTHORSHIP

Yes, Thanks.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 12:04 PM
To: nfiner@ucsd.edu; Wally Carlo, M.D.; mcw3@po.cwru.edu; alaptook@WIHRI.org; Abhik Das (adas@rti.org); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; mgantz@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

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Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: SUPPORT AUTHORSHIP
Date: Monday, November 23, 2009 1:19:25 PM

From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Nov 23 13:17:25 2009
Subject: RE: SUPPORT AUTHORSHIP

Yes, but I hope this does not open the floodgates!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 23, 2009 1:04 PM
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; alaptook@WIHRI.org; Das, Abhik; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT AUTHORSHIP
Importance: High

Hi
A request is being made to include a second author, Ambal, from University of Alabama on both SUPPORT papers. As you are probably aware, Alabama was the highest recruiter in the trial with 184 of the 1316 infants enrolled. Ambal took charge of SUPPORT recruitment when Wally was not available and was instrumental in the performance at the Alabama site.

Please send me a yes/no vote to include Ambal by 11/25

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Cc: "Finer, Neil"
Subject: RE: Authorship for SUPPORT Trials
Date: Monday, November 23, 2009 12:38:00 PM

Wally
The manual lists you at the UAB PI for the Study. In view of the phenomenal recruitment, I can send an email vote to the subcommittee for concurrence with adding Ambal – would this be ok?? Let me know so I can do this quickly

Thanks
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 23, 2009 12:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.; Finer, Neil
Subject: Authorship for SUPPORT Trials

Dear Rose:

I noticed that Ambal is not on our list of authors. I apologize for noticing this so late in the process but Ambal was instrumental in recruiting infants and following the protocol particularly when I am out of town. Please let me know if there is a problem in adding him as an author to both papers.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Monday, November 23, 2009 12:04 PM
To: Gantz, Marie; Abhik Das; Wally Carlo; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT CPAP Final??

Thanks Marie
This is fine
I would still prefer not to have the ROP data by strata and to replace the Death/ROP with ROP only for our Table 3
Thanks Neil

On 11/23/09 8:55 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

> Neil,
>
> I apologize if I was confusing about the ROP outcome. ROP was
> determined at the point at which an eye exam met criteria for final
> status. This could have been in the hospital or as an outpatient, and
> at no time was the outcome cut-off (at transfer, discharge, etc.).
> However, the outcome of survival is survival to discharge, 1 year of
> life, or in a few cases transfer because status after transfer was
> unknown per the GDB forms. I looked into the three cases where status
> after transfer was unknown, and found that one infant was seen at 18
> month FU, one infant was transferred to a chronic care facility at 6
> months (18 month FU window not yet open), and the last infant was
> transferred at 3 months and is listed as lost to FU for the 18 month
> visit because of noncompliance with last contact after 2 years of age
> (although the infant was not explicitly noted to be alive at that time
> on the NF12). Only this last infant is missing final ROP status - the
> other two met criteria for the positive ROP outcome (no severe ROP). I hope this helps clear things up.
>
> Marie
>
>
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Sunday, November 22, 2009 2:43 PM
> To: Das, Abhik; Gantz, Marie; Wally Carlo; Rich, Wade; Higgins,
> Rosemary
> (NIH/NICHD) [E]
> Subject: SUPPORT CPAP Final??
>

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> Hi Everyone
> Here is my final
> I have largely ignored Jon's comments
> We were over words with Marie and Abhiks additions so I shortened them
> and other parts. I removed the number of analyses to save words.
> Marie, I would like in Table 3 to replace ROP or Death with ROP in
> survivors. ROP or death is not a postulate of SUPPORT that I would
> report when Wally's paper is going in.
> I have removed ROP from the Stratum tables - it is too uncertain when
> it includes ROP at discharge or transfer Have a look and make any
> further changes you think are essential. We are within the specified
> limits.
> I will be travelling Tuesday but I can upload with Wades help anytime.
> Thanks to you all - This has been a journey!!!
> Neil

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From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: adas@rti.org
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF
Date: Monday, November 23, 2009 7:18:35 AM
Attachments: SUPPORT NEJM Nov12 Final-oshea edits.doc

Neil,

Congratulations on completing this trial - an amazing accomplishment. In the attached I offer a few editing suggestions.

In Table 1, I would not include p values, as these are pre-randomization variables and the interpretation of a non-significant p value is that the difference between groups is not larger than can be explained by chance. But since we know that any differences are explained by chance (i.e., randomization), why do we need p values.

In Table 2, I would not include p values, as any differences cannot be attributed to chance, as they are processes that were prescribed by the protocol with the intention of being different.

In Table 3 I would round the p value to one significant digit.

Thanks so much for your efforts.

Mike

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Sent: Sat 11/14/2009 2:38 AM
To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu'; 'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu'; (b) (6) 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; 'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu'; 'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu'; 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu'; Michael O`Shea; 'mcaplan@northshore.org'; 'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu'; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org'; 'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-
Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----

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From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 17:06:37 2009
Subject: CPAP vs SURF

Wally and Rose
Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were opposite so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
Neil

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Suggested additions

Suggested deletions

[redacted]

Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Vivek Narendran, MD MRCP[8]; Edward Donovan[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA;

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[10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22] University of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

Neil N Finer, M.D.

University of California at San Diego

402 Dickinson St., MPF 1-140

San Diego, CA 92103-8774

Phone: (919) 543 3285

Fax: (619) 543 3812

Email: nfiner@ucsd.edu

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP is an effective evidence based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm $H_2$0. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of **usual** care. There was a significant increase in the occurrence of pneumothoraxces [redacted] in the CPAP group (9.1% vs 3.0%, p=.001), most occurring **especially** within the first 2 days, consistent with the findings of an earlier meta analysis**Error! Bookmark not defined.**, **balanced by** and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks.

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In the SUPPORT Trial **we compared** [redacted] early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen. [redacted]

The primary hypothesis of this trial was that **among infants of 24 to 27 weeks gestation, early CPAP and a protocol driven limited ventilator strategy, with continuing CPAP in the NICU, as compared to** [redacted] prophylactic/early surfactant and conventional ventilation, [redacted] will [redacted] survival without BPD at 36 weeks.

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Eligible infants were **those born at** 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP **device** methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 > **0**.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean

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airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN

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baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment, as this introduced a clustering effect into the design, and increased the sample sizes **further** by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered **to detect** for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which **We** assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but **for infants who required < 30% oxygen at 36 weeks we** required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks.[1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed, **at four points in time,** the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-

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DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant, was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 05% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm,(RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

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Strata Results: 24 – 25 weeks Gestation

CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. [redacted] The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP intitiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in

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the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

Our trial differs from the recently reported COIN trial[10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included; the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately

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powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal [redacted] steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence

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of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Saturday, November 21, 2009 11:20 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: CPAP draft with statistical methods edits

Marie
I am concerned about any ROP outcome that uses status at Transfer or discharge – unless the infants were judged to be mature by this time- If you have this data and that is what your reporting please let me know. I would not report the ROP outcomes by strata in the CPAP paper. There is indeed far too much missing data and for many infants final eye status was > 55 weeks so that transfer or discharge is a relatively useless time point. Let's leave the ROP to the SpO2 paper.
I am concerned about the number of infants with missing ROP data in this paper and I fear that the reviewers will also be concerned about this. Lets get these papers in and see what they say
Thanks
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, November 20, 2009 3:17 PM
To: Finer, Neil
Cc: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: CPAP draft with statistical methods edits

Neil,

Attached is your paper and tables with edits by Abhik and myself. Note that, as in the SpO2 paper, I have re-run the test of the ROP outcome so that it looks at survivors only. Interestingly, that test now favors surfactant in the 26-27 week GA stratum with a p-value of .03. However, since we have so much missing ROP data I would not want to read that much into it, especially since the death or ROP outcome is not significant.

There is one additional edit I did not make to the paper, but which I think is worth considering. Someone on the subcommittee call (I can't remember who) brought up the distinction between "need for oxygen" vs "oxygen use." In terms of how we actually defined BPD in our data, we looked at oxygen use because that is what we capture. Need for oxygen, as the person pointed out on the call, might be more in line with what is captured by the physiologic definition. This is supported by the statement in your paper that the physiologic definition "required demonstration of oxygen dependence by an attempt at oxygen withdrawal." Food for thought.

I will be sending you a new CONSORT figure that includes BPD as well as death so it will match the new version I will be sending Wally that includes ROP and the number of infants missing the final ROP outcome.

Thanks, and have a good weekend.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Tyson, Jon E
Subject: RE: significant p values
Date: Friday, November 20, 2009 10:49:07 AM

Jon
Thank you for your thoughtful comments. As far as reporting the primary outcomes for each paper, neither were significant, so we are following what was written in the protocol regarding the p of 0.02 to be conservative. There was no difference between the two groups, so we are fine with reporting the primary outcome. With respect to the secondary outcomes, there was no p value stated in the protocol for statistical significance. We will report the p values and the RR's with the CI's for the respective secondary outcomes. Since there are no p values indicated in the protocol for secondary outcomes, we can state "signiificant at $p < 0.05$" and be well within the bounds of the protocol. The reader/reviewer can then make their own judgement with respect to the data. The predefined primary outcome analysis is with center, familial clustering and GA strata taken into consideration as described in the protocol. At this point, corrections for further multiple comparisons, though potentially helpful, are likely to hold up reporting of the primary and secondary study outcomes. These data needs to be promptly submitted for publication.

As far as soliciting assistance from independent statisticians, this is something that should have gone through the subcommittee and steering committee. In the vast majority of cases, the steering committee is open and receptive to such assistance. However, this could be perceived by some as undermining the network processes in place. I know that you are very invested in the NRN activities and are passionate about having our results presented in an honest and accurate way.

For the Bayesian analyses, a secondary proposal can be submitted to the SUPPORT Subcommittee. This was not part of the original protocol and would cause a delay in getting the primary papers submitted if we await a proposal, try to set up a call, and review the proposal to include this in the primary papers.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Tyson, Jon E [Jon.E.Tyson@uth.tmc.edu]
Sent: Thursday, November 19, 2009 4:51 PM
To: Wally Carlo, M.D.; Finer, Neil; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: significant p values

Neil, the alpha of 5% would refer to the combined alpha error of the two components (CPAP/limited ventilation vs. intubation/surfactant; high vs low O2 sat goals). The p of 0.02 was labelled as conservative because it was slightly less than 0.025 which added to another 0.025 would be a 0.05 total alpha error for both components combined).

Without indicating what I thought, I copied pg 22-24 and provided these pages independently to two statisticians and asked each to indicate based on the material in the protocol, what p would be considered signficant for the primary outcome and what p would be signfiicant for the secondary outcomes. Each concluded that the protocol

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indicated the p value considered signficant for the primary outcome would be 0.02 and the p value for secondary outcomes was unstated and ambiguous. Each noted that an argument could be made that if the p for the primary outcome needed to be corrected for multiple comparsions, it was logically inconsistent to use a higher p for secndary outcomes when many more comparisons were performed for seconddary outcomes in each of the two components However, it is true that most studies report what is referred to as a nominal p value of 0.05 for secondary outcomes.

It seems to me that it would be good to perform Bayesian analyses for the primary analyses, death, and when the 18 mo analyses are performed, death or impairment. As we have discussed before, Bayesian analyses have been recommened as supplementary analyses for all clinical trials (Wijeysundera et al J Clin Epi 2009;62:13-2), and they largely, if not entirely, avoid the problems of rather arbitrary decisions about what p values should be considered signficant and whether to correct for mulitple comparisons. I think these would support conclusions currently based on the p values that are being debated and as in the Phototherapy trial, could be conservatively perfromed, described in two sentences in the text and provided in the Appendix for the groups combined and for the two GA strata. Claudia Pedroza could do these promptly. Neil and Wally, how does this sound to you? I'm of course happy to talk about this if you want.

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 18, 2009 5:19 PM
To: Finer, Neil; Tyson, Jon E; Abhik Das; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: <no subject>

I agree. That is how it was interpreted at the time

Wally

-----Original Message-----
From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, November 18, 2009 6:57 PM
To: Jon Tyson <Jon.E.Tyson@uth.tmc.edu>; Abhik Das <adas@rti.org>; Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Rich, Wade <wrich@ucsd.edu>
Subject: <no subject>

Hi Jon
I have read page 23 and I am unclear. In 2 places it clearly states that alpha is 5%
The 2% appears to refer to calculations for determining sample size or possibly for the interaction tests.
I will wait for Abhik to review
Thanks
Neil

Here is page 23

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.
With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in

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the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

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Higgins, Rosemary (NIH/NICHD) [E]

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Thursday, November 19, 2009 7:04 PM
To: Tyson, Jon E
Cc: Wally Carlo, M.D.; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: significant p values

Thanks Jon
Has the network previously done such analyses?
Abhik can we talk about this
Neil

Sent from my iPhone

On Nov 19, 2009, at 2:51 PM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:

> Neil, the alpha of 5% would refer to the combined alpha error of the
> two components (CPAP/limited ventilation vs. intubation/surfactant;
> high vs low O2 sat goals). The p of 0.02 was labelled as conservative
> because it was slightly less than 0.025 which added to another 0.025
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> protocol indicated the p value considered signficant for the primary
> outcome would be 0.02 and the p value for secondary outcomes was
> unstated and ambiguous. Each noted that an argument could be made that
> if the p for the primary outcome needed to be corrected for multiple
> comparsions, it was logically inconsistent to use a higher p for
> secndary outcomes when many more comparisons were performed for
> seconddary outcomes in each of the two components However, it is true
> that most studies report what is referred to as a nominal p value of
> 0.05 for secondary outcomes.
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> the primary analyses, death, and when the 18 mo analyses are
> performed, death or impairment. As we have discussed before, Bayesian
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> clinical trials (Wijeysundera et al J Clin Epi 2009;62:13-2), and they
> largely, if not entirely, avoid the problems of rather arbitrary
> decisions about what p values should be considered signficant and
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> Appendix for the groups combined and for the two GA strata. Claudia
> Pedroza could do these promptly. Neil and Wally, how does this sound
> to you? I'm of course happy to talk about this if you want.
>
> Jon E. Tyson, MD, MPH
> Center for Clinical Research & Evidence-Based Medicine UT Medical
> School at Houston
> 6431 Fannin St., MSB 2.106
> Houston, TX 77030
> voice 713-500-5651
> fax 713-500-0519
>
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Wednesday, November 18, 2009 5:19 PM
> To: Finer, Neil; Tyson, Jon E; Abhik Das; Wally Carlo; Higgins,
> Rosemary (NIH/NICHD) [E]; Rich, Wade
> Subject: RE: <no subject>
>
> I agree. That is how it was interpreted at the time
>
> Wally
>
> -----Original Message-----
> From: Finer, Neil <nfiner@ucsd.edu>
> Sent: Wednesday, November 18, 2009 6:57 PM
> To: Jon Tyson <Jon.E.Tyson@uth.tmc.edu>; Abhik Das <adas@rti.org>;
> Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]
> <higginsr@mail.nih.gov>; Rich, Wade <wrich@ucsd.edu>
> Subject: <no subject>
>
> Hi Jon
> I have read page 23 and I am unclear. In 2 places it clearly states
> that alpha is 5% The 2% appears to refer to calculations for
> determining sample size or possibly for the interaction tests.
> I will wait for Abhik to review
> Thanks
> Neil
>
> Here is page 23
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> tailed alpha level test of 5% and for powers of 80% and 90%. The N1
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> With regard to the power for detecting the interaction between the two
> factors in the factorial, a fourfold increase in the stated sample
> size would be required to detect an interaction effect as large or
> larger as that stated in the table (i.e. the Detectable Difference),
> assuming the same alpha level and power. The interaction effect

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> NDI is considered as a secondary outcome then the table below gives
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> two outcomes, we chose a conservative 2% level of significance and a
> conservative outcome rate of 50% in making the calculations. These
> sample sizes are given in the N1 column and would also allow a 10%
> difference in NDI/death to be detected with a power of 73%. If an 80%
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> sample sizes in the N2 column.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: SUPPORT small group call
Date: Thursday, November 19, 2009 2:58:00 PM

Great
Thanks
Rose

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, November 19, 2009 2:58 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT small group call

ok

Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Thursday, November 19, 2009 2:57 PM
To: wacarlo@uab.edu <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; 'Das, Abhik' <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; 'Poole Kenneth (E-mail)' <poo@rti.org>
Cc: 'Cassandra Hudson' <chudson@peds.uab.edu>
Subject: SUPPORT small group call

Hi,
We will have the call tomorrow morning at 9 am ET (6 AM PT)

Call in number 866-675-(b) (6) with pass code (b) (6)

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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301-496-5575
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higginsr@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Request for conflict of interest information for NEJM
Date: Thursday, November 19, 2009 2:41:00 PM

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, November 19, 2009 2:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for conflict of interest information for NEJM

I have no conflicts of interest.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; Gantz, Marie; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Das, Abhik; Poole, W. Kenneth; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) [redacted]; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Cc: "Gantz, Marie"
Subject: RE: SUPPORT analyses
Date: Thursday, November 19, 2009 11:38:00 AM

OK
I am waiting to hear from Wally and will call his office
Rose

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, November 19, 2009 11:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT analyses

Yes, did you not get my email (and another from Robin) on this?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 19, 2009 11:26 AM
To: Das, Abhik; Gantz, Marie; 'Wally Carlo, M.D.'
Subject: FW: SUPPORT analyses

Can you make this time?

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, November 19, 2009 11:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT analyses

Thanks Rose
Can you set up a call at 9:00Eastern AM and send me a call in? I would limit the call to 1 hour or shorter,
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 19, 2009 7:56 AM
To: Finer, Neil; 'adas@rti.org'
Cc: 'wcarlo@peds.uab.edu'
Subject: Re: SUPPORT analyses

I am available today except 2-330 and tomorrow until 130 pm ET

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Das, Abhik <adas@rti.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Thu Nov 19 10:53:15 2009
Subject: RE: SUPPORT analyses

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Hi Abhik
How about you, me and Rose and Wally if available
I appreciate your concern and I will accept ultimate responsibility.
Thanks Abhik
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, November 19, 2009 7:51 AM
To: Finer, Neil
Subject: RE: SUPPORT analyses

I fully share your concerns, and am quite upset at the way this has unfolded. I can do a call at 9 am EST tomorrow. Who else do you want on the call?

It is clear from Ken's email to me (attached), that he does not consider this to be an issue.

Thanks

Abhik

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, November 19, 2009 10:41 AM
To: Das, Abhik
Subject: RE: SUPPORT analyses

Abhik
I will be available - I am in Denver as visiting professor so my day is very full, I will try to accommodate a call. I will tied up tomorrow till 2:00PM and I fly at 3:00PM Could we have a call around 7:00AM here - about 9:00AM Eastern tomorrow am.
I think we need this call even if Wally is unavailable I am the PI and bear the responsibility.
I am concerned that we are being attacked from within with broad circulation before it was sent to us.
Does Ken believe that was room for interpretation??
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, November 19, 2009 7:29 AM
To: Finer, Neil; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT analyses

If we decide to follow the advice from Dennis, we can present the p values as is for death and other secondary outcomes, without interpretation as to statistical significance. The trends remain regardless of what cut-point one chooses to use.

Again, I agree with you and Wally (and Ken) that I had not seen this as an issue because I had viewed the 2% significance assumed for the sample size calculations as something we used to conservatively size the trial, which would not affect the analysis. However, the reactions from Jon and

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Dennis now suggest that there may be NEJM reviewers as well who feel differently about this. So, we need to figure out how to proceed. Rose tells me that Wally is out of the country; so I don't know whether he can participate in a call today or tomorrow.

Thanks

Abhik

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, November 19, 2009 10:20 AM
To: Das, Abhik; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT analyses

Abhik
To understand what we need to do - as neither primary is significant do we add to the statistical sections of the methods that we chose a p value =0.02 for the primary? I'm not sure why we can the use a lesser p value for other outcomes like death. Why would we be allowed to do that - what is the logic of a lesser significance level for these??
We need to figure this out
Certainly I was not aware nor where you or Marie about the need for the p to be 0.02 How did we miss this - I have read that section as calculations to develop sample size. Lets arrange a call and figure this out I'll wait for your answers Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, November 19, 2009 7:09 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT analyses

I agree with your interpretation that the analysis was always planned to be at the 0.05 level, but unfortunately the protocol is not explicit about that in the analysis plan, and the NEJM reviewers, if they are nitpicking about it (which they sometimes are), could make an issue out of it. You already have the contrary views on this from Jon and Dennis in previous emails.

As for why 0.02 and not 0.025, I don't have a good answer for that, and one would have to ask Ken, because he did those calculations. Perhaps he was thinking of apportioning the significance at 0.02 each for death/BPD and death/ROP, and 0.01 for death/NDI, to get to an overall trial-wise significance of 0.05.

Thanks

Abhik

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, November 19, 2009 9:58 AM
To: Das, Abhik; Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie

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Subject: RE: SUPPORT analyses

Abhik and ALL.

As I understood, the p 0.02 was to power the triasl but the analysis was always planned to be 0.05 as these were always thought to be 2 trials.

Why would we have used 0.02 instead of 0.025 for the effect? No one ever takes 0.04. Indeed, we planned two separate primary hypotheses as these were meant to be two separate trials.

Wally

-----Original Message-----
From: Das, Abhik <adas@rti.org>
Sent: Thursday, November 19, 2009 10:35 AM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Gantz, Marie <mgantz@rti.org>
Subject: SUPPORT analyses

Neil and Wally:

We may need a conference call amongst ourselves to resolve the issue of the significance level for the analyses. I heard back from Ken on this issue (his perspective is crucial because he designed the statistical aspects of the trial), and here is what he had to say:

"... We chose the 0.02 level to adjust for the primary outcomes (BPD/death,ROP/death). We could have chosen the less conservative 0.025 but did not. It has nothing to do with the secondary outcomes. And it should have nothing to do with "significance" of the final test of the primary outcomes. They are what they are and should be reported as such."

I agree with Ken that it is ok to use conservative criteria to adequately size a trial, but then use conventional significance levels in the analysis. However, since this was not articulated explicitly in the protocol analysis plan, Dennis sees merit in Jon's arguments on this, and thinks that we may have trouble with the NEJM in this regard. Here is the approach he proposes:

"... simply do the primary short-term outcome (death/ROP) at the 0.02 level (since that appears to be the planned outcome) and describe all other tests that we do as tests of secondary hypotheses for which the p-values are reported descriptively at the per-test level with no interpretation of statistical significance. That would seem to me to avoid the problem entirely."

Materially, whatever approach we take doesn't make much difference because our primary outcome results are not significant either way. Let me know how you want to proceed.

Thanks

Abhik

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-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 18, 2009 6:19 PM
To: Finer, Neil; Jon Tyson; Das, Abhik; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: <no subject>

I agree. That is how it was interpreted at the time

Wally

-----Original Message-----
From: Finer, Neil <nfiner@ucsd.edu>
Sent: Wednesday, November 18, 2009 6:57 PM
To: Jon Tyson <Jon.E.Tyson@uth.tmc.edu>; Abhik Das <adas@rti.org>; Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Rich, Wade <wrich@ucsd.edu>
Subject: <no subject>

Hi Jon
I have read page 23 and I am unclear. In 2 places it clearly states that alpha is 5% The 2% appears to refer to calculations for determining sample size or possibly for the interaction tests.
I will wait for Abhik to review
Thanks
Neil

Here is page 23

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.
With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).
If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: Antenatal_Consent_Paper_Network_Final
Date: Thursday, November 19, 2009 8:39:00 AM
Attachments: Antenatal_Consent_Paper_Network_Final.doc

Hi,
Here is the antenatal consent paper; the antenatal consent was a secondary study to SUPPORT and authored by the coordinators. I will likely have close to final drafts of the two main SUPPORT papers in the next few days.

Thanks for all you help.

Rose

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Antenatal Consent in a Large Multicenter Trial - At What Cost?

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Short title: Antenatal Consent in a Large Multicenter Trial

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Keywords: Informed Consent, Antenatal, Neonatal

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Gradý Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

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Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

ABSTRACT

Background

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The purpose of this study was to quantify the time, effort, and rate of success involved obtaining antenatal consent to enroll infants into the Neonatal Research Network SUPPORT trial, and to determine if these infants were representative of the eligible population.

Methods

Eligible subjects were those likely to deliver in the SUPPORT gestational age window (24-27 6/7 wks). Data included who approached them for consent, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled in the trial. In addition, all eligible, non-enrolled infants entered into the NRN Generic Database (GDB) throughout the period of SUPPORT enrollment were identified to allow comparison of all infants enrolled in SUPPORT to those who were eligible but not enrolled.

Results

2826 women were identified at 18 sites between October 2005 and February 2009. 2228 were approached for consent and 1219 (54.7%) agreed. For 76.9% of those approached, < 3 visits were required to complete the consent process. (mean 2.0 +/- 1.2). Of the 659 consented infants delivered within the study window, 611 of were enrolled. Mothers who received a neonatal consult were more likely to give consent ($p<.001$). Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached (n=2290) to those whose mothers were approached (n=2082), the percentage of infants not exposed to steroids was significantly greater in the non-approached vs. the approached group (20.0%, 3.4% $p<.001$).

Conclusions:

In a trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver in the GA window for each one who delivered an enrolled infant. The differences between enrolled and non-enrolled infants highlight difficulties in attempting to recruit a representative population for trials requiring antenatal consent.

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Introduction:

Informed consent ensures that subjects enrolled in research trials are appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery.

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation in which a site is paid based on the number of subjects enrolled. Funds may be awarded for screening for eligible subjects, but centers are not usually paid for the time required to seek or obtain consent for subjects who are not enrolled. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

The early months of enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that the number of patients enrolled seemed to be much lower than the number screened. Thus, this secondary study was designed to quantify the antenatal screening and consent process to determine the time, effort and other factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network. The second objective of the study was to determine whether the subjects enrolled in the trial were representative of the overall eligible population.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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second half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early Continuous Positive Airway Pressure (CPAP) initiated in the delivery room to early intubation and surfactant given within the first hour of life, in a 2x2 factorial design with randomization to two different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were those inborn at NRN centers at 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was planned. SUPPORT enrollment began in February 2005 and ended in February 2009.

Eligible subjects for the antenatal consent secondary study were those women whom the Obstetrical/Perinatal staff thought were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (RTI International, Research Triangle Park, NC). Research staff collected study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts that were made by the research coordinator/RN, and whether permission from the obstetrician was obtained to approach for antenatal consent. Because a neonatal consult is often performed as part of clinical management in this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached were asked if they were asked to participate in any other studies for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the Data Coordinating Center. As part of the ongoing NRN Generic Database (GDB) observational

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study, data were routinely collected on inborn infants at NRN centers, including most of those who met the gestational age eligibility criteria for the SUPPORT study. These data were used to identify eligible non-enrolled (non-consented) infants and to evaluate whether infants enrolled in the SUPPORT trial represented the eligible NRN population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment met enrollment criteria for participation in SUPPORT. Eligible but non-enrolled infants had information collected on prenatal care, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT. These data were used to determine whether all eligible women were approached and if not, what the reasons for not approaching them were.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2826 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two NRN centers did not participate in the antenatal consent trial and 4 participating centers did not identify 50 eligible women who delivered in the GA window between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Thirteen centers had more than 50 women deliver in the GA window (range 51 to 90) before they stopped collecting data. All data collected by participating centers have been included in this analysis. Analysis

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using only the first 50 women from the centers that over-enrolled was not significantly different. Screening, enrollment and consent numbers by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Mothers were considered unable to give consent when in active labor, too young, or having either a mental or physical health issue which precluded them being approached.

A study coordinator or research RN made 74.7% of all approaches. For 76.9% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1219 (54.7%) gave consent, and 581 subsequently delivered within the SUPPORT study window. Of these, 536 delivered infants who were enrolled (Figure 2). Forty-eight of the 659 consented infants born in the GA window (7.3%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 69.7% of cases where the parent(s) were approached for consent. Mothers receiving a neonatal consult were more likely to consent ($p < .001$), but consent was obtained during the consult in only 11.6%.

Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose mothers were approached revealed several important differences (Table 2). Infants of approached mothers were significantly more likely to be non-Hispanic white; to be older, and to have a high school education , private medical insurance, and at least one PNC visit. A significantly higher proportion of eligible infants whose mothers were not approached had no exposure to antenatal

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steroids compared with infants whose mothers were approached (20.0% vs 3.4%, p<.001). Maternal parity was lower in women who were approached, but gravidity was not significantly different between the groups.

Eligible GDB infants who were not enrolled in SUPPORT and those who were enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance and to have received prenatal care and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%) (Table 3).

Discussion:

To our knowledge this is the first study to evaluate the time and efforts required to approach and obtain antenatal consent from parents for the enrollment of their unborn infants. Our results reveal that 5 families needed to be identified and screened for every one infant successfully enrolled. Only 47.7% of women consented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.6) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.6 hours. Assuming that the enrollment rate of the SUPPORT trial was equivalent before data collection for the antenatal consent study began suggests that over 2400 hours were spent screening greater than 6000 women and approaching nearly 4800 for consent to enroll 1316 infants in the SUPPORT trial. This estimate includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found

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that only 8.4% of women reported having been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT gestational age window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. The approached vs. non-approached data help us to better understand what part of the population never had an opportunity to be part of the enrollment, and what the reasons were. The enrollment data allow us to compare the population that was enrolled in the trial with those who were eligible but not enrolled. This is the ultimate result of the consent process.

Infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which collected data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items.[4,5] The standards require a flow chart of participants to quantify eligible populations but it does not require identifying the demographics of the non-enrolled group or its similarity to the enrolled or consented populations. Following the CONSORT standards in all antenatal consent trials, that is, obtaining basic demographic information for all eligible infants, will help us understand whether similar reduction biases in enrollment occurs in other studies.

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Blinding of allocation has always been the benchmark for protecting trials from biased enrollment. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[6] However, these controls only protect the trial from internal bias, not the selection bias we have seen. It does not affect the external validity or generalizability of the findings to non-study patients. Manning and Silverman have voiced concerns about this type of selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[7,8] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [9] In a study of recruitment and retention of premature infants into an early intervention trial, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [10,11] In our study, the sociodemographic variables tended to favor the enrolled group. Mitchell and Kline showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13] In our study, the socio-demographic variables tended to favor the enrolled group.

Our analysis would suggest that under-privileged subjects were less likely to participate. Because this trial included subjects from 18 academic centers with long-term experience in randomized trials and a broad mix of racial, ethnic, and socio-economic populations, it is not likely that the bias represents an intention to include or exclude any group. The logical conclusion is that the many subjects who were not enrolled in this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[14], suggest that it may be ethically appropriate to allow trials that compare routinely used interventions to waive

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the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population enrolled as a result of antenatal consent may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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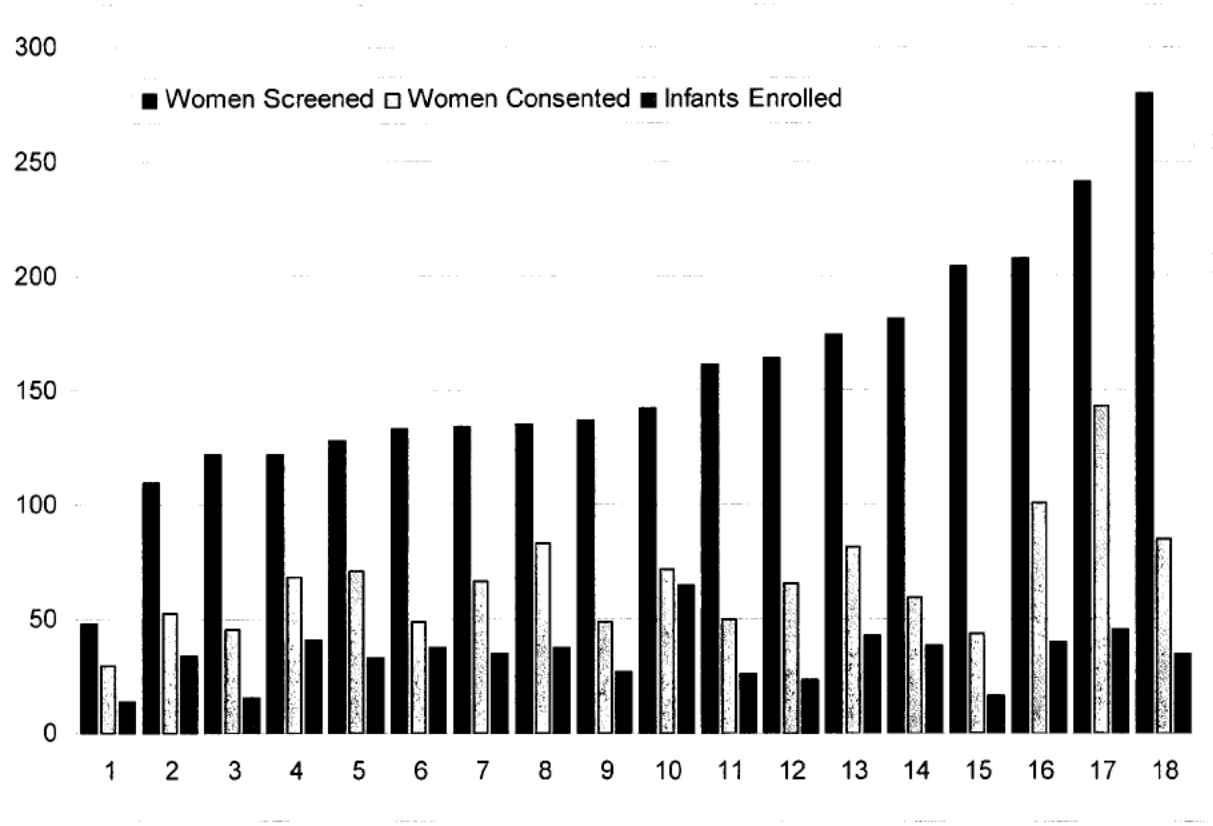

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.5
Insufficient time	119	19.9
Study staff unavailable	37	6.2
Consult not done	17	2.8
Not aware of admission	35	5.9
Other	321	53.7

Table 1. Reasons for not approaching mothers for consent.

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	Infants whose Mothers were Approached N=2082	Infants whose Mothers were Not Approached N=2290	p Value
Maternal age (Mean ± SD)	27.5 ± 6.4	26.9 ± 6.8	0.0071
White-Non Hispanic	853 (41.0%)	774 (33.9%)	<0.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0844
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0463
≥ HS Education	1134 (75.3%)	1090 (68.3%)	<0.0001
Self Pay/Uninsured	130 (6.3%)	228 (10.0%)	<0.0001
At Least 1 PN Visit	2015 (96.8%)	2112 (92.4%)	<0.0001
No Antenatal Steroids	71 (3.4%)	457 (20.0%)	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Enrolled Infants N=1316	Non-Enrolled Infants N=3056	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.2 ± 6.7	0.7107
White-Non Hispanic	521 (39.7%)	1106 (36.3%)	0.0329
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9438
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7725
≥ HS Education	708 (74.1%)	1516 (70.61%)	0.0490
Self Pay/Uninsured	81 (6.2%)	227 (9.1%)	0.0012
At Least 1 PN Visit	1263 (96.0%)	2864 (93.9%)	0.0052
No Antenatal Steroids	50 (3.8%)	478 (15.7%)	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

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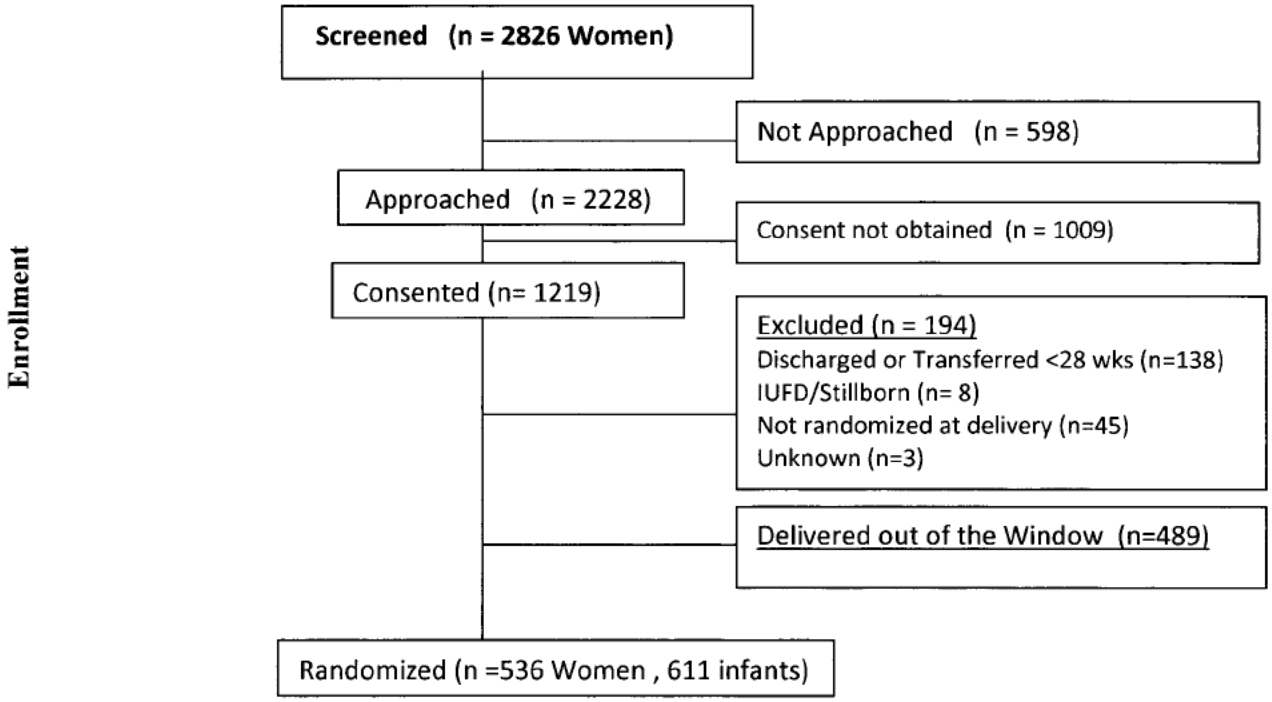

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Antenatal_Consent_Paper_Network_Final
Date: Thursday, November 19, 2009 8:37:00 AM
Attachments: Antenatal_Consent_Paper_Network_Final.doc

This can go for clearance

Rose

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Thursday, November 19, 2009 8:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Antenatal_Consent_Paper_Network_Final

Rose,
Here is the Antenatal paper with the approved boilerplate included.
wade

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Antenatal Consent in a Large Multicenter Trial - At What Cost?

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

ABSTRACT

Background

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The purpose of this study was to quantify the time, effort, and rate of success involved obtaining antenatal consent to enroll infants into the Neonatal Research Network SUPPORT trial, and to determine if these infants were representative of the eligible population.

Methods

Eligible subjects were those likely to deliver in the SUPPORT gestational age window (24-27 6/7 wks). Data included who approached them for consent, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled in the trial. In addition, all eligible, non-enrolled infants entered into the NRN Generic Database (GDB) throughout the period of SUPPORT enrollment were identified to allow comparison of all infants enrolled in SUPPORT to those who were eligible but not enrolled.

Results

2826 women were identified at 18 sites between October 2005 and February 2009. 2228 were approached for consent and 1219 (54.7%) agreed. For 76.9% of those approached, < 3 visits were required to complete the consent process. (mean 2.0 +/- 1.2). Of the 659 consented infants delivered within the study window, 611 of were enrolled. Mothers who received a neonatal consult were more likely to give consent ($p<.001$). Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached (n=2290) to those whose mothers were approached (n=2082), the percentage of infants not exposed to steroids was significantly greater in the non-approached vs. the approached group (20.0%, 3.4% $p<.001$).

Conclusions:

In a trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver in the GA window for each one who delivered an enrolled infant. The differences between enrolled and non-enrolled infants highlight difficulties in attempting to recruit a representative population for trials requiring antenatal consent.

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Introduction:

Informed consent ensures that subjects enrolled in research trials are appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery.

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation in which a site is paid based on the number of subjects enrolled. Funds may be awarded for screening for eligible subjects, but centers are not usually paid for the time required to seek or obtain consent for subjects who are not enrolled. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

The early months of enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that the number of patients enrolled seemed to be much lower than the number screened. Thus, this secondary study was designed to quantify the antenatal screening and consent process to determine the time, effort and other factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network. The second objective of the study was to determine whether the subjects enrolled in the trial were representative of the overall eligible population.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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second half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early Continuous Positive Airway Pressure (CPAP) initiated in the delivery room to early intubation and surfactant given within the first hour of life, in a 2x2 factorial design with randomization to two different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were those inborn at NRN centers at 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was planned. SUPPORT enrollment began in February 2005 and ended in February 2009.

Eligible subjects for the antenatal consent secondary study were those women whom the Obstetrical/Perinatal staff thought were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (RTI International, Research Triangle Park, NC). Research staff collected study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts that were made by the research coordinator/RN, and whether permission from the obstetrician was obtained to approach for antenatal consent. Because a neonatal consult is often performed as part of clinical management in this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached were asked if they were asked to participate in any other studies for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the Data Coordinating Center. As part of the ongoing NRN Generic Database (GDB) observational

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study, data were routinely collected on inborn infants at NRN centers, including most of those who met the gestational age eligibility criteria for the SUPPORT study. These data were used to identify eligible non-enrolled (non-consented) infants and to evaluate whether infants enrolled in the SUPPORT trial represented the eligible NRN population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment met enrollment criteria for participation in SUPPORT. Eligible but non-enrolled infants had information collected on prenatal care, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT. These data were used to determine whether all eligible women were approached and if not, what the reasons for not approaching them were.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2826 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two NRN centers did not participate in the antenatal consent trial and 4 participating centers did not identify 50 eligible women who delivered in the GA window between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Thirteen centers had more than 50 women deliver in the GA window (range 51 to 90) before they stopped collecting data. All data collected by participating centers have been included in this analysis. Analysis

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using only the first 50 women from the centers that over-enrolled was not significantly different. Screening, enrollment and consent numbers by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Mothers were considered unable to give consent when in active labor, too young, or having either a mental or physical health issue which precluded them being approached.

A study coordinator or research RN made 74.7% of all approaches. For 76.9% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1219 (54.7%) gave consent, and 581 subsequently delivered within the SUPPORT study window. Of these, 536 delivered infants who were enrolled (Figure 2). Forty-eight of the 659 consented infants born in the GA window (7.3%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 69.7% of cases where the parent(s) were approached for consent. Mothers receiving a neonatal consult were more likely to consent ($p < .001$), but consent was obtained during the consult in only 11.6%.

Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose mothers were approached revealed several important differences (Table 2). Infants of approached mothers were significantly more likely to be non-Hispanic white; to be older, and to have a high school education , private medical insurance, and at least one PNC visit. A significantly higher proportion of eligible infants whose mothers were not approached had no exposure to antenatal

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steroids compared with infants whose mothers were approached (20.0% vs 3.4%, p<.001). Maternal parity was lower in women who were approached, but gravidity was not significantly different between the groups.

Eligible GDB infants who were not enrolled in SUPPORT and those who were enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance and to have received prenatal care and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%) (Table 3).

Discussion:

To our knowledge this is the first study to evaluate the time and efforts required to approach and obtain antenatal consent from parents for the enrollment of their unborn infants. Our results reveal that 5 families needed to be identified and screened for every one infant successfully enrolled. Only 47.7% of women consented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.6) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.6 hours. Assuming that the enrollment rate of the SUPPORT trial was equivalent before data collection for the antenatal consent study began suggests that over 2400 hours were spent screening greater than 6000 women and approaching nearly 4800 for consent to enroll 1316 infants in the SUPPORT trial. This estimate includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found

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that only 8.4% of women reported having been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT gestational age window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. The approached vs. non-approached data help us to better understand what part of the population never had an opportunity to be part of the enrollment, and what the reasons were. The enrollment data allow us to compare the population that was enrolled in the trial with those who were eligible but not enrolled. This is the ultimate result of the consent process.

Infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which collected data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items.[4,5] The standards require a flow chart of participants to quantify eligible populations but it does not require identifying the demographics of the non-enrolled group or its similarity to the enrolled or consented populations. Following the CONSORT standards in all antenatal consent trials, that is, obtaining basic demographic information for all eligible infants, will help us understand whether similar reduction biases in enrollment occurs in other studies.

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Blinding of allocation has always been the benchmark for protecting trials from biased enrollment. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[6] However, these controls only protect the trial from internal bias, not the selection bias we have seen. It does not affect the external validity or generalizability of the findings to non-study patients. Manning and Silverman have voiced concerns about this type of selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[7,8] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [9] In a study of recruitment and retention of premature infants into an early intervention trial, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [10,11] In our study, the sociodemographic variables tended to favor the enrolled group. Mitchell and Kline showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13] In our study, the socio-demographic variables tended to favor the enrolled group.

Our analysis would suggest that under-privileged subjects were less likely to participate. Because this trial included subjects from 18 academic centers with long-term experience in randomized trials and a broad mix of racial, ethnic, and socio-economic populations, it is not likely that the bias represents an intention to include or exclude any group. The logical conclusion is that the many subjects who were not enrolled in this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[14], suggest that it may be ethically appropriate to allow trials that compare routinely used interventions to waive

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the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population enrolled as a result of antenatal consent may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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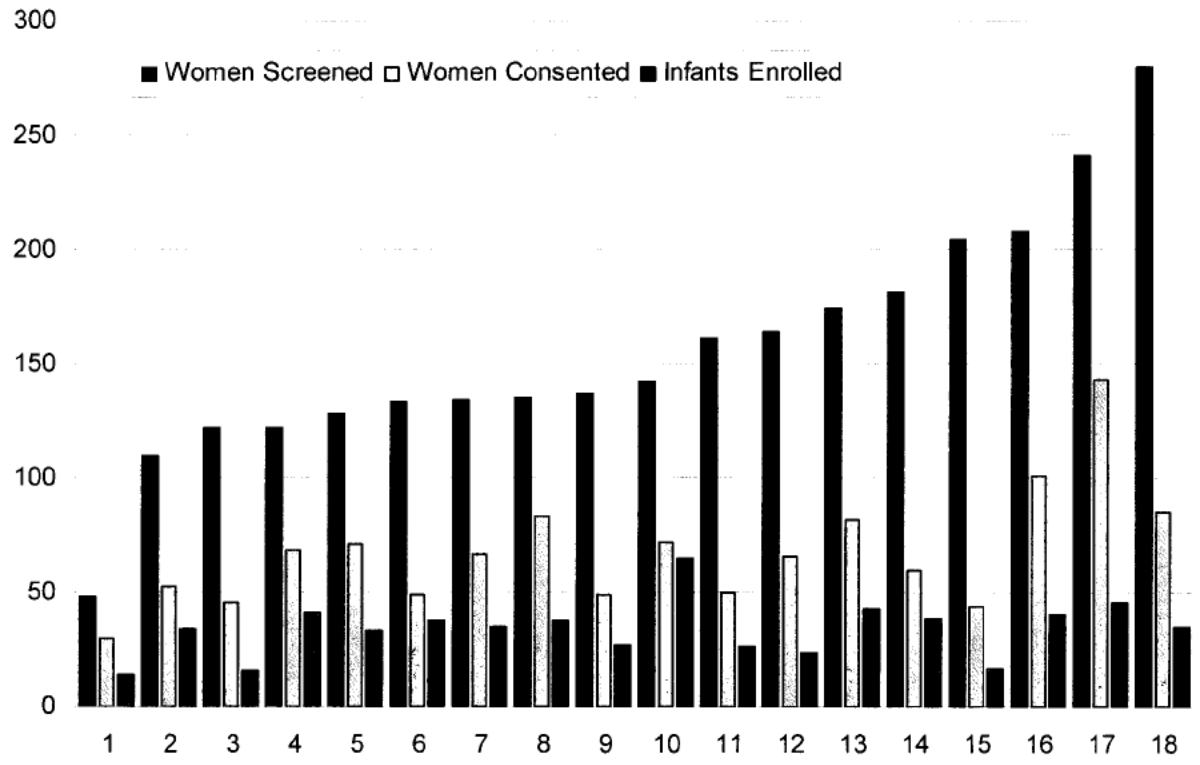

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.5
Insufficient time	119	19.9
Study staff unavailable	37	6.2
Consult not done	17	2.8
Not aware of admission	35	5.9
Other	321	53.7

Table 1. Reasons for not approaching mothers for consent.

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	Infants whose Mothers were Approached N=2082	Infants whose Mothers were Not Approached N=2290	p Value
Maternal age (Mean ± SD)	27.5 ± 6.4	26.9 ± 6.8	0.0071
White-Non Hispanic	853 (41.0%)	774 (33.9%)	<0.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0844
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0463
≥ HS Education	1134 (75.3%)	1090 (68.3%)	<0.0001
Self Pay/Uninsured	130 (6.3%)	228 (10.0%)	<0.0001
At Least 1 PN Visit	2015 (96.8%)	2112 (92.4%)	<0.0001
No Antenatal Steroids	71 (3.4%)	457 (20.0%)	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Enrolled Infants N=1316	Non-Enrolled Infants N=3056	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.2 ± 6.7	0.7107
White-Non Hispanic	521 (39.7%)	1106 (36.3%)	0.0329
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9438
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7725
≥ HS Education	708 (74.1%)	1516 (70.61%)	0.0490
Self Pay/Uninsured	81 (6.2%)	227 (9.1%)	0.0012
At Least 1 PN Visit	1263 (96.0%)	2864 (93.9%)	0.0052
No Antenatal Steroids	50 (3.8%)	478 (15.7%)	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

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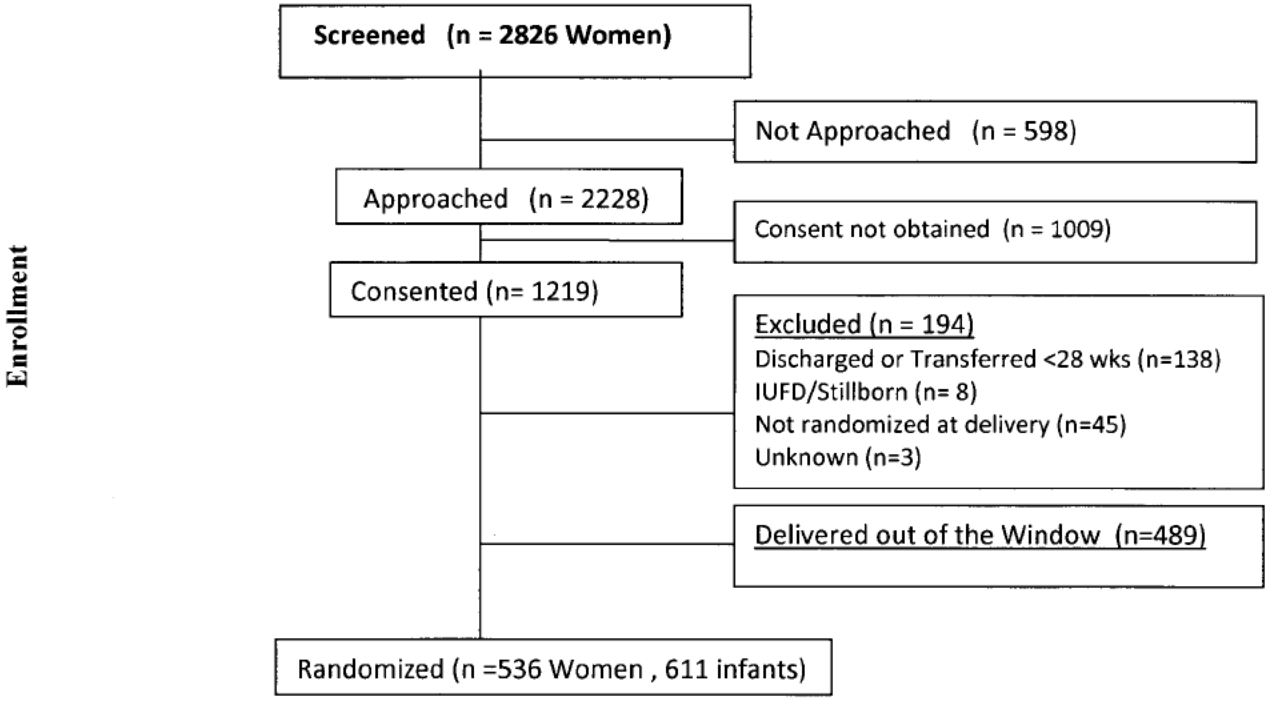

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Boilerplates | SUPPORT
Date: Wednesday, November 18, 2009 3:34:00 PM
Attachments: Boilerplate, Carlo, SUPPORT Oximetry, 2009-11-18.doc
Boilerplate, Finer, SUPPORT Ventilation, 2009-11-18.doc

From: Higgins, Rosemary (NIH/NICHD) [E]
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To: nfiner@ucsd.edu; wacarlo@uab.edu
Subject: FW: Boilerplates | SUPPORT

Here are the most recent versions of the boilerplates. You can remove the conflict of interest tables.

Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, November 18, 2009 2:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Boilerplates | SUPPORT

Just to be sure. Here are the latest boilerplate files with the title page and acknowledgements.

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@uab.edu"
Subject: FW: Request for Dr. Solomon NEJM
Date: Wednesday, November 18, 2009 2:42:00 PM
Attachments: Dr Solomon inquiry adrev.doc

Are you ok with this??

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, November 17, 2009 12:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Request for Dr. Solomon NEJM

Small suggested changes are inserted in the attached. Should we also say that ideally we would like to see both papers published in the same issue, or do we not want to go there?

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 12:19 PM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for Dr. Solomon NEJM

Hi,
Attached is a brief request from Dr. Solomon at NEJM. Let me know if you have specific comments. I can send it to her before the week is out!!
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
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Dear Dr. Solomon

The NICHD NRN has recently completed a large multicenter SUPPORT Trial (SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants) with over 1300 infants enrolled into the study.

This prospective, randomized, factorial 2X2 design trial had two main hypotheses:
1). Relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a ~~permissive~~ protocol defined ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.
2). Relative to infants managed with a higher more conventional SpO2 range (91% to 95%) ~~SpO2 range~~ that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

~~This is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors tested are:~~
~~1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (< 1 hour) surfactant and mechanical ventilation.~~
~~2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.~~

We have two separate papers focusing on the two separate arms of the factorial design ~~, each of which addresses on of the two primary outcomes from the two original hypotheses (ventilation strategy and oximetry)~~ addressing each of the two hypotheses above. We intend to submit both papers to the NEJM. ~~Are~~ Please let me know if there are any special guidelines for reporting studies with factorial designs set forth by NEJM.~~?~~ Your assistance is appreciated in advance.

Best regards,

Rosemary D. Higgins, MD on behalf of the NICHD Neonatal Research Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: CPAP vs SURF
Date: Wednesday, November 18, 2009 2:27:00 PM
Attachments: Boilerplate, Carlo, SUPPORT Oximetry, 2009-11-16.doc
Boilerplate, Finer, SUPPORT Ventilation, 2009-11-16.doc

Are these the final boilerplates – they have the DSMC – the document that Neil sent didn't have it

Thanks
Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Monday, November 16, 2009 10:10 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu'; 'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu'; (b) (6) 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; 'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu'; 'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu'; 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'moshea@wfubmc.edu'; 'mcaplan@northshore.org'; 'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu'; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org'; 'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: 'kzaterka@rti.org'; 'mcunningham@rti.org'; 'petrie@rti.org'
Subject: RE: CPAP vs SURF

Attached is also the current author list for the title page and boilerplate for both papers. If you have any changes, please let me by the end of TODAY.

I will copy and paste the information from these files into the final manuscript drafts after the call this afternoon.

Stephanie

Stephanie Wilson Archer

The Eunice Kennedy Shriver

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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, November 14, 2009 2:39 AM
To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu'; 'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu'; (b) (6) 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; 'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu'; 'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu'; 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'moshea@wfubmc.edu'; 'mcaplan@northshore.org'; 'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu'; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org'; 'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-

Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----

From: Finer, Neil <nfiner@ucsd.edu>

To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>

Sent: Thu Nov 12 17:06:37 2009

Subject: CPAP vs SURF

Wally and Rose

Here is the "final" CPAP vs Surf paper

It fits NEJM and incorporates all suggestions although some were opposite so we made some choices.

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Please review

Wally can you make sure our definitions for BPD etc are identical??

Thanks

I would like to get these submitted

Please share with me your thoughts

Be well

Neil

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SUPPORT Oximetry (without FU)

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Acknowledgements

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We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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University of New Mexico Health Sciences Center (U10 HD53089, GCRC M01 RR997) - Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN.

University of Rochester Medical Center Golisano Children's Hospital (U10 HD40521, GCRC M01 RR44) - Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, GCRC M01 RR633) - Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) - Seetha Shankaran, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (U10 HD27871, CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022) - Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Data and Safety Monitoring Committee - Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), RTI International; Dorothy B. Gail, PhD,

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National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger, PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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SUPPORT Ventilation (without FU)

Neil N. Finer, MD[1]
Waldemar A. Carlo, MD[2]
Michele C. Walsh, MD MS[3]
Wade Rich, RRT[1]
Marie Gantz, PhD[4]
Abbot R. Laptook, MD[5]
Bradley A. Yoder, MD[6]
Roger G. Faix, MD[6]
Abhik Das, PhD[7]
W. Kenneth Poole, PhD[4]
Kurt Schibler, MD[8]
Edward F. Donovan, MD[8]
Nancy S. Newman, RN[3]
Ivan D. Frantz III, MD[9]
Susie Buchter, MD[10]
Pablo J. Sánchez, MD[11]
Kathleen A. Kennedy, MD MPH[12]
Nirupama Laroia, MD[13]
Brenda B. Poindexter, MD MS[14]
C. Michael Cotten, MD MHS[15]
Krisa P. Van Meurs, MD[16]
Shahnaz Duara, MD[17]
Vivek Narendran, MD MRCP[8]

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[2] Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL
[3] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH
[4] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC
[5] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[6] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[8] Department of Pediatrics, University of Cincinnati, Cincinnati, OH
[9] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA
[10] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[11] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX
[12] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[13] University of Rochester Medical Center, Golisano Children's Hospital, Rochester, NY
[14] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN
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[17] University of Miami Miller School of Medicine, Miami, FL

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Edward F. Bell, MD[20]
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Kristi L. Watterberg, MD[22]
Rosemary D. Higgins, MD[23]
for the NICHD Neonatal Research Network

Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Case Western Reserve University Rainbow Babies & Children's Hospital (U10 HD21364, GCRC M01 RR80) - Avroy A. Fanaroff, MD; Bonnie S. Siner, RN.

---

[18] Department of Pediatrics, Wayne State University, Detroit, MI
[19] Wake Forest University School of Medicine, Winston-Salem, NC
[20] Department of Pediatrics, University of Iowa, Iowa City, IA
[21] Department of Pediatrics, Yale University School of Medicine, New Haven, CT
[22] University of New Mexico Health Sciences Center, Albuquerque, NM
[23] Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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Higgins, Rosemary (NIH/NICHD) [E]

From: Rich, Wade <wrich@ucsd.edu>
Sent: Wednesday, November 18, 2009 10:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Tyson, Jon E; Wally_Carlo_M.D.; Walsh, Michele
Cc: 'mgantz@rti.org'
Subject: RE: CPAP - Surf Manuscript

We used the approved boilerplate provided to us by Stephanie on November 16, and added a few authors at your request. If there is a more current one, I have not seen it.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 18, 2009 6:15 AM
To: Finer, Neil; Tyson, Jon E; Wally_Carlo_M.D.; Walsh, Michele
Cc: 'mgantz@rti.org'; Rich, Wade
Subject: RE: CPAP - Surf Manuscript

Neil
A couple of comments:
The GA strata analysis probably should be stated as post-hoc.

We should also include a sentence or two about the fact that the surfactant trials particularly the prophylactic trials, were performed in the pre-antenatal corticosteroid era of MFM/neonatology management (late 1980's and NIH consensus conference on antenatal steroids was 1995). Our population had a very high rate of antenatal steroid exposure.

The grant support for each site should list the U10 awards first, followed by the other support. There is no mention of our DSMC in the acknowledgements - did Stephanie send an updated title page for this?? I had asked that this be done.

Thanks for the tremendous effort!!

Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20592
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Finer, Neil [nfiner@ucsd.edu]
Sent: Tuesday, November 17, 2009 10:50 PM
To: Tyson, Jon E; Wally_Carlo_M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele
Cc: 'mgantz@rti.org'; Rich, Wade
Subject: CPAP - Surf Manuscript

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Hi Jon, Michele, Wally and Rose
I am sending this version for your review. I have not sent it to a wider audience as I would like your views first. This version is NEJM compatible - I think - Perhaps a little sterile but I'll wait for your replies There were many errors, typos and I rewrote quite a bit. I think some of this was from trying to accommodate 15-20 other rewrites. I appreciate everyone's efforts and contribution. No one will need to feel they did not contribute to this manuscript - even with 29 authors.
I have used the Tables so that I haven't quoted the stats but refer to the Tables and included Marie's Consort Diagram and the New Tables As always thanks Marie As for the rest of you - here is your next meal - don't get indigestion!
Neil

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT COI responses
Date: Wednesday, November 18, 2009 10:11:52 AM

Is that all?? Amazing!!!

From: Archer, Stephanie (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 18 10:10:04 2009
Subject: SUPPORT COI responses

Still missing responses from:

Wally
Marie
Kurt
Mike Cotten

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nxs5@case.edu"
Subject: Re: Request for conflict of interest information for NEJM
Date: Wednesday, November 18, 2009 9:54:35 AM

Yes
Thanks
Rose

----- Original Message -----
From: Nancy Newman <nxs5@case.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 18 09:52:28 2009
Subject: RE: Request for conflict of interest information for NEJM

Hi Rose- I realized that but thought I had already responded for the CPAP paper. Are the revised papers going to be circulated again?
Thanks.....NN

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 18, 2009 9:46 AM
To: Nancy Newman
Subject: RE: Request for conflict of interest information for NEJM

Nancy
Since there are two papers, we asked twice - once for Neil's paper and once for Wally's paper.

thansk
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Nancy Newman [nxs5@case.edu]
Sent: Wednesday, November 18, 2009 9:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for conflict of interest information for NEJM

I thought I sent this already but if not- I don not have any conflict of interest for the SUPPORT Oximetry paper.....Nancy Newman

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

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Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: CPAP - Surf Manuscript
Date: Wednesday, November 18, 2009 9:14:43 AM
Attachments: SUPPORT NEJM Nov17 09.doc
NEJM Tables Nov 17 09.doc

Stephanie -
I thought Neil was sent an updated version for the title page and acknowledgements to re-order the grant support (with U10's first) and to list the DSMC members. I don't have access to old emails right now, but I thought we took care of this, right??

Let me know - perhaps I should sent him the updated title page/acknowledgements??

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Finer, Neil [nfiner@ucsd.edu]
Sent: Tuesday, November 17, 2009 10:50 PM
To: Tyson, Jon E; Wally_Carlo_M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele
Cc: 'mgantz@rti.org'; Rich, Wade
Subject: CPAP - Surf Manuscript

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I have used the Tables so that I haven't quoted the stats but refer to the Tables and included Marie's Consort Diagram and the New Tables
As always thanks Marie
As for the rest of you - here is your next meal – don't get indigestion!
Neil

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcomes of death or BPD, using the physiologic definition and death or BPD using the need for supplemental oxygen at 36 weeks were non-significantly reduced in the CPAP group compared to the surfactant group, when adjusted for gestational age, center and familial clustering ((47.8% vs. 51%, Relative risk(RR) =0.95 (0.85, 1.05) p=0.304, 48.7% vs. 54.1%, RR=0.91 (0.82, 1), p=0.072). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001).

Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in preterm infants.[12] Overall prophylactic surfactant has not been reported to significantly reduce BPD alone , whereas early compared with selective later surfactant has been associated with a decreased risk of chronic lung disease.[2] Surfactant not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS.[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[7,8,9]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[11], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks was non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that in infants of 24 to 27 weeks gestation the use of early CPAP and a protocol driven strategy of limited ventilation with continuing CPAP in the NICU infants will result in an increased survival without BPD at 36 weeks compared to infants managed with surfactant within an hour of birth, and a subsequent conventional ventilator strategy.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by a conventional ventilation strategy.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were

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randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant

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patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP $\leq$ 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition

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after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from February 2005 through February 2009. There were 565 infants enrolled in the lower gestational age strata (24 0/7 to 25 6/7 wks), and 751 in the higher strata 26 0/7 to 27 6/7 wks) (Figure). There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

Data regarding delivery room interventions is provided in Table 2. Fewer CPAP infants received positive pressure ventilation in the delivery room compared with the surfactant infants. The Surfactant group received significantly more epinephrine. Intubation in the DR was significantly decreased in the CPAP infants, and 32.9% of CPAP infants never received surfactant during their hospitalization (Table 2).

The primary outcome of death or BPD, using either the physiologic definition or the need for supplemental oxygen at 36 weeks post menstrual age did not reach statistical significance when adjusted for gestational age, center and familial clustering as pre-specified (Table 3).

Death during the hospitalization was non-significantly lower for the CPAP group overall. There was no significant difference in the occurrence of BPD using either the Physiologic Definition or the need for oxygen at 36 weeks (Table 3).

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There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (Table 3). The incidence of severe retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[15] or need for surgical intervention for ROP was not different between the CPAP compared to the surfactant infants (Table 3).

Strata Results: 24 – 25 weeks Gestation

CPAP infants in this strata had a significantly lower mortality while hospitalized 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034 (Appendix Table A1). Causes of death for this strata are reported in Table 4. There was a significantly higher exposure to postnatal steroids for BPD for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants.

26-27 weeks Gestation

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There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, and significantly fewer CPAP infants received postnatal steroids for BPD (Appendix Table 2A).

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in very preterm infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported trial of Morley et al[10~~15~~] in that we randomized all eligible preterm infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth and a conventional strategy. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that units with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation.[4,5,6] The infants who received surfactant were treated with a ventilator approach that was used by a majority of NRN

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units before the trial began. We believed that comparing these two methods would provide more clinically relevant results.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. The randomization resulted in a balance between the infants randomized to each intervention within the pre-specified gestational age strata (Figure, Table 1). While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was not associated with any increase in death or BPD, or in any adverse neonatal outcomes. BPD using either the physiologic definition or the need for oxygen at 36 weeks was decreased but these differences were not statistically significant. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata. While we did not postulate such a difference in the individual strata this increased occurrence of death is cause for concern resulting in a number

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needed to harm of 12.2 infants for each additional death among surfactant treated infants. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP have a non significant reduction in the incidence of death or BPD, with no demonstrable increase in any adverse neonatal outcome when compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth. Multiple secondary outcomes including death in the immature strata favored the CPAP group. CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Figure 1 – Consort Diagram

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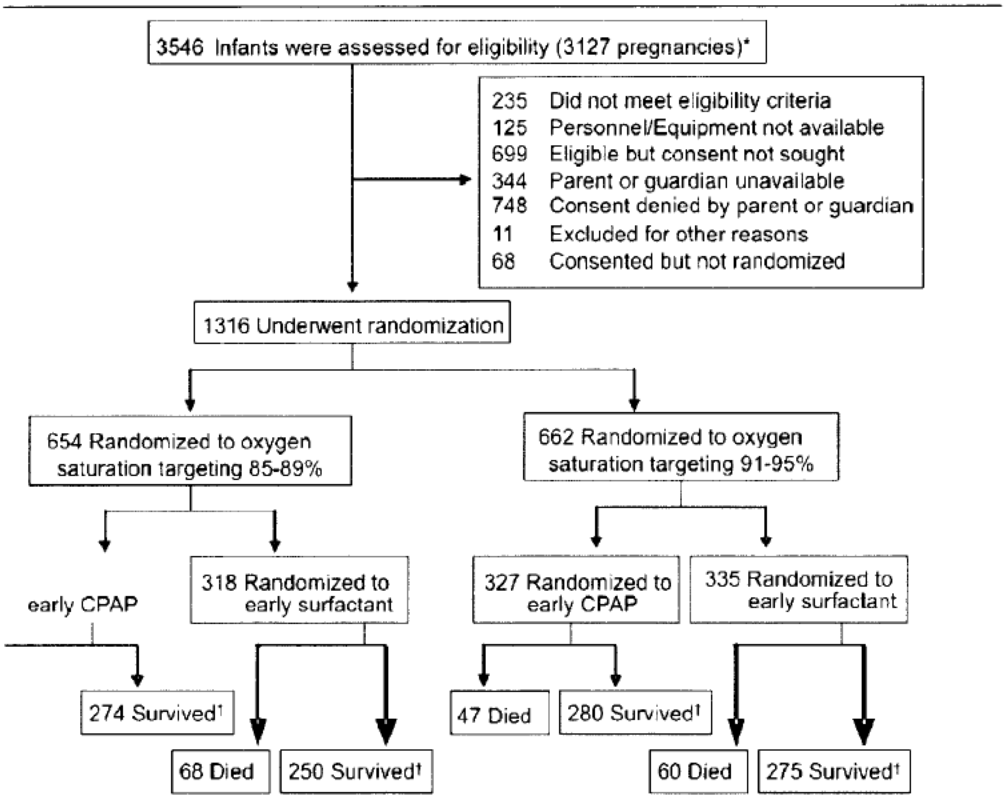

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)
	26-27	57.0% (378/663)	57.1% (373/653)
Randomized to Low SpO2 in 2x2 factorial	24-25 weeks GA	49.8% (142/285)	47.9% (134/280)
	26-27 weeks GA	51.3% (194/378)	49.3% (184/373)
Male		51.6% (342/663)	56.7% (370/653)
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)
	Hispanic	20.8% (138/663)	18.5% (121/653)
	Other/unknown	3.2% (21/663)	4.0% (26/653)
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1
Antenatal steroids (any)		96.8% (642/663)	95.6% (623/652)
Antenatal steroids (full course)		73.6% (486/660)	69.8% (453/649)
Death in the DR (per SUPP03/SUPP04)		0.2% (1/663)	0.8% (5/653)

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661	25.6% (167/653	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662	92.9% (606/652	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663	22.4% (146/653	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660	93.4% (609/652	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660	27.0% (176/652	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU	67.1% (443/660	98.9% (646/653	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	47.8% (317/663)	51.0% (333/653)	0.95 (0.85, 1.05)	0.3039
BPD (supplemental oxygen) or death by 36 weeks PMA	48.7% (323/663)	54.1% (353/653)	0.91 (0.83, 1.01)	0.0719
Death while hospitalized or severe ROP	28.4% (176/620)	32.1% (193/601)	0.87 (0.74, 1.03)	0.0971
BPD (physiologic definition) by 36 weeks PMA	39.2% (223/569)	40.6% (219/539)	0.99 (0.87, 1.14)	0.9172
BPD (supplemental oxygen) by 36 weeks PMA	40.2% (229/569)	44.3% (239/539)	0.94 (0.82, 1.06)	0.3178
Severe ROP	13.5% (70/517)	14.2% (68/480)	0.95 (0.7, 1.28)	0.7406
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Death by 36 weeks PMA	14.2% (94/663)	17.5% (114/653)	0.81 (0.63, 1.03)	0.0890
Death at any time while hospitalized	16.4% (109/663)	19.6% (128/653)	0.84 (0.67, 1.05)	0.1259
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
Discharge on oxygen	22.2% (122/550)	23.9% (124/519)	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)	0.0111
Any air leak in first 14 days	6.8% (45/663)	7.4% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. Cause of Death - 24-25 week Strata

Variable	Category	CPAP (N=68)	Surfactant (N=90)
Contributory cause of death	1=RDS	13/68 (19.1)	31/90 (34.4)
	2=BPD	10/68 (14.7)	7/90 (7.8)
	3=Infection	14/68 (20.6)	15/90 (16.7)
	4=NEC	10/68 (14.7)	16/90 (17.8)
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)
	6=Immaturity	3/68 (4.4)	5/90 (5.6)
	7=Other	7/68 (10.3)	11/90 (12.2)

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Appendix Tables

Table A1. Outcomes for 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.4470
BPD (supplemental oxygen) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.3578
Death while hospitalized or severe ROP	42.1% (112/266)	55.2% (144/261)	0.74 (0.62, 0.89)	0.0015
BPD (physiologic definition) by 36 weeks PMA	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.4570
BPD (supplemental oxygen) by 36 weeks PMA	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.5329
Severe ROP	23.3% (47/202)	31.4% (55/175)	0.75 (0.54, 1.05)	0.0994
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.0125
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Total LOS any hospital* Mean±StdErr (N=407)	122.0 ± 2.9	119.0 ± 3.1		0.4690
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table A2. Outcomes for 26 to 27 week Strata

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.4828
BPD (supplemental oxygen) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.1163
Death while hospitalized or severe ROP	18.1% (64/354)	14.4% (49/340)	1.25 (0.88, 1.77)	0.2153
BPD (physiologic definition) by 36 weeks PMA	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.4621
BPD (supplemental oxygen) by 36 weeks PMA	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.0812
Severe ROP	7.3% (23/315)	4.3% (13/305)	1.86 (0.94, 3.67)	0.0728
Death in the first week	4.0% (15/378)	2.7% (10/373)	1.36 (0.61, 3.02)	0.4561
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.6055
Death at any time while hospitalized	10.8% (41/378)	10.2% (38/373)	1.06 (0.7, 1.6)	0.7966
Total LOS any hospital* Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4		0.2147
Days on supplemental oxygen† Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9		0.0349
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3		0.0848
Discharge on oxygen	15.8% (53/336)	19.6% (65/331)	0.88 (0.64, 1.2)	0.4118
Alive and off MV (HFV/CV) at 7 days	71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.1016
Any air leak in first 14 days	5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.9652
Medical or surgical NEC	10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.1353
PDA requiring surgery	7.2% (27/374)	6.0% (22/368)	1.22 (0.7, 2.14)	0.4875
IVH grade 3-4	10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.1732
Postnatal steroids for BPD	2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.0076

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Wednesday, November 18, 2009 6:18:04 AM

----- Original Message -----
From: Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 20:10:03 2009
Subject: RE: Request for conflict of interest information for NEJM

I have no conflicts of interest related to this study.

Bradley A. Yoder, MD
Professor of Pediatrics
University of Utah School of Medicine
Medical Director, University Hospital NICU
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Phone: 801-581-7052
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 9:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Bradley Yoder; Roger Faix; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20592
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From: Finer, Neil
To: Tyson, Jon E; Wally, Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele
Cc: "mgantz@rti.org"; Rich, Wade
Subject: CPAP - Surf Manuscript
Date: Tuesday, November 17, 2009 10:50:44 PM
Attachments: SUPPORT NEJM Nov17 09.doc
NEJM Tables Nov 17 09.doc

Hi Jon, Michele, Wally and Rose

I am sending this version for your review. I have not sent it to a wider audience as I would like your views first. This version is NEJM compatible – I think – Perhaps a little sterile but I'll wait for your replies

There were many errors, typos and I rewrote quite a bit. I think some of this was from trying to accommodate 15-20 other rewrites. I appreciate everyone's efforts and contribution. No one will need to feel they did not contribute to this manuscript – even with 29 authors.

I have used the Tables so that I haven't quoted the stats but refer to the Tables and included Marie's Consort Diagram and the New Tables

As always thanks Marie

As for the rest of you - here is your next meal – don't get indigestion!

Neil

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Death while hospitalized or severe ROP	28.4% (176/620)	32.1% (193/601)	0.87 (0.74, 1.03)	0.0971
BPD (physiologic definition) by 36 weeks PMA	39.2% (223/569)	40.6% (219/539)	0.99 (0.87, 1.14)	0.9172
BPD (supplemental oxygen) by 36 weeks PMA	40.2% (229/569)	44.3% (239/539)	0.94 (0.82, 1.06)	0.3178
Severe ROP	13.5% (70/517)	14.2% (68/480)	0.95 (0.7, 1.28)	0.7406
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Death by 36 weeks PMA	14.2% (94/663)	17.5% (114/653)	0.81 (0.63, 1.03)	0.0890
Death at any time while hospitalized	16.4% (109/663)	19.6% (128/653)	0.84 (0.67, 1.05)	0.1259
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
Discharge on oxygen	22.2% (122/550)	23.9% (124/519)	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)	0.0111
Any air leak in first 14 days	6.8% (45/663)	7.4% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. Cause of Death - 24-25 week Strata

Variable	Category	CPAP (N=68)	Surfactant (N=90)
Contributory cause of death	1=RDS	13/68 (19.1)	31/90 (34.4)
	2=BPD	10/68 (14.7)	7/90 (7.8)
	3=Infection	14/68 (20.6)	15/90 (16.7)
	4=NEC	10/68 (14.7)	16/90 (17.8)
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)
	6=Immaturity	3/68 (4.4)	5/90 (5.6)
	7=Other	7/68 (10.3)	11/90 (12.2)

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Appendix Tables

Table A1. Outcomes for 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.4470
BPD (supplemental oxygen) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.3578
Death while hospitalized or severe ROP	42.1% (112/266)	55.2% (144/261)	0.74 (0.62, 0.89)	0.0015
BPD (physiologic definition) by 36 weeks PMA	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.4570
BPD (supplemental oxygen) by 36 weeks PMA	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.5329
Severe ROP	23.3% (47/202)	31.4% (55/175)	0.75 (0.54, 1.05)	0.0994
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.0125
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Total LOS any hospital* Mean±StdErr (N=407)	122.0 ± 2.9	119.0 ± 3.1		0.4690
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table A2. Outcomes for 26 to 27 week Strata

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.4828
BPD (supplemental oxygen) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.1163
Death while hospitalized or severe ROP	18.1% (64/354)	14.4% (49/340)	1.25 (0.88, 1.77)	0.2153
BPD (physiologic definition) by 36 weeks PMA	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.4621
BPD (supplemental oxygen) by 36 weeks PMA	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.0812
Severe ROP	7.3% (23/315)	4.3% (13/305)	1.86 (0.94, 3.67)	0.0728
Death in the first week	4.0% (15/378)	2.7% (10/373)	1.36 (0.61, 3.02)	0.4561
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.6055
Death at any time while hospitalized	10.8% (41/378)	10.2% (38/373)	1.06 (0.7, 1.6)	0.7966
Total LOS any hospital* Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4		0.2147
Days on supplemental oxygen† Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9		0.0349
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3		0.0848
Discharge on oxygen	15.8% (53/336)	19.6% (65/331)	0.88 (0.64, 1.2)	0.4118
Alive and off MV (HFV/CV) at 7 days	71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.1016
Any air leak in first 14 days	5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.9652
Medical or surgical NEC	10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.1353
PDA requiring surgery	7.2% (27/374)	6.0% (22/368)	1.22 (0.7, 2.14)	0.4875
IVH grade 3-4	10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.1732
Postnatal steroids for BPD	2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.0076

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs. 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs. 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

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Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis**Error! Bookmark not defined.**. A reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

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The primary outcome of death or BPD at 36 weeks was showed non-significantly reduced in the CPAP arm, 33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19)

The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, use of early CPAP and a protocol driven strategy of limited ventilation in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to

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provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant

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patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP < 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition

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after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. In the delivery room, surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, $p=0.072$) when adjusted for gestational age, center and familial clustering as pre-specified. Death during the hospitalization

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was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Tables 3 and 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids

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for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

Our trial differs from the recently reported trial of Morley et al [10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing and

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enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP as used in this trial have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. CPAP as used in this trial is an effective evidence-based alternative to intubation and surfactant for very preterm infants.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 7:56:46 PM

----- Original Message -----
From: Roger Faix <Roger.Faix@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 19:47:54 2009
Subject: RE: Request for conflict of interest information for NEJM

Hi Rose!

I have no conflicts.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 9:44 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Bradley Yoder; Roger Faix; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 6:25:53 PM

----- Original Message -----
From: Michael O`Shea <moshea@wfubmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 17:32:12 2009
Subject: RE: Request for conflict of interest information for NEJM

No, I have no conflicts of interests.

Mike O'Shea

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 11/17/2009 11:44 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Michael O`Shea; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Brenda Morris"
Subject: RE: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 4:48:00 PM

Yes
Thanks
Rose

From: Brenda Morris [mailto(b) (6)
Sent: Tuesday, November 17, 2009 4:45 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for conflict of interest information for NEJM

No for me..... Did you get my email with the comments about Neil's paper??? Brenda

> From: higginsr@mail.nih.gov
> To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; nxs5@cwru.edu; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; b(b) (6) Nirupama_Laroia@URMC.Rochester.edu; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; Vivek.Narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; higginsr@mail.nih.gov
> CC: archerst@mail.nih.gov
> Date: Tue, 17 Nov 2009 11:44:48 -0500
> Subject: Request for conflict of interest information for NEJM
>
> Hi,
> You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 3:55:00 PM

-----Original Message-----
From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Tuesday, November 17, 2009 3:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for conflict of interest information for NEJM

No, AL

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; Laptook, Abbot; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
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Rosemary D. Higgins, MD
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From: Finer, Neil
To: Gantz, Marie; Abhik Das; Wally Carlo; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, November 17, 2009 3:45:03 PM

Thanks Marie
I would favor just what you have - a single unadjusted p value
Thanks
Neil

On 11/17/09 12:09 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

> Neil and Wally,
>
> Attached are two versions of the CONSORT figure that incorporate both
> treatment arms as well as new versions of Neil's tables with the changes
> discussed on the call yesterday.
>
> The only thing I have been unable to do is produce an adjusted p-value
> for cause of death. The reason is that there are so many causes of death
> and so many centers to control for that the statistical model will not
> converge. I would suggest the following options:
>
> 1) Use the unadjusted p-value or do not report one.
> 2) I can fit a model with center as a random effect (as opposed to a
> fixed effect as has been done for all the other adjusted models),
> ignoring the familial clustering. This test, like the unadjusted
> p-value, is non-significant for the treatment effect, and use of this
> test would require another sentence to be added to the methods since a
> different modeling procedure would be used.
> 3) I can test for differences with respect to a specific cause of death,
> such as BPD.
>
> Let me know what you want to do.
>
> Thanks,
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, November 17, 2009 1:29 PM
> To: Gantz, Marie; Das, Abhik; Wally Carlo; Rich, Wade; Higgins, Rosemary
> (NIH/NICHD) [E]
> Subject: SUPPORT
>
> HI Marie
> When you send the revised Tables, please include the p value for the
> death/Physiologic definition and for the ROP/Death as I do not have

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> these from the Tables you previously sent Oct 27
> Thanks
> Neil

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 1:53:43 PM

From: Piazza, Anthony J <apiazza@emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 13:50:45 2009
Subject: RE: Request for conflict of interest information for NEJM

No
I do not have any conflict of interest with the publication of this manuscript

Anthony J Piazza, MD
Assistant Professor of Pediatrics
Assistant Med Director Neonatal Services, Children's Healthcare of Atlanta
at Egleston Hospital
Director of Outreach and Community Services
Emory Division of Neonatal-Perinatal Medicine
Office: 404-778-1450
Fax: 404-778-1467
apiazza@emory.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:53 AM
To: Piazza, Anthony J; wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; Anthony Piazza; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM

Hi,
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Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 1:24:38 PM

----- Original Message -----
From: Laroia, Nirupama <Nirupama_Laroia@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 13:09:00 2009
Subject: RE: Request for conflict of interest information for NEJM

I have no conflict of interest. Thanks.
Nirupama Laroia

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; Phelps, Dale; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
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Thanks
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Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:44:03 PM

----- Original Message -----
From: Frantz, Ivan <ifrantz@tuftsmedicalcenter.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 12:41:37 2009
Subject: RE: Request for conflict of interest information for NEJM

None.

Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; Frantz, Ivan; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:40:01 PM

----- Original Message -----
From: Poindexter, Brenda B <bpoindex@iupui.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 12:39:43 2009
Subject: RE: Request for conflict of interest information for NEJM

No conflicts
Brenda

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; Poindexter, Brenda B; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

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Rosemary D. Higgins, MD
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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Request for Dr. Solomon NEJM
Date: Tuesday, November 17, 2009 12:36:25 PM
Attachments: Dr Solomon inquiry adrev.doc

Small suggested changes are inserted in the attached. Should we also say that ideally we would like to see both papers published in the same issue, or do we not want to go there?

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 12:19 PM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for Dr. Solomon NEJM

Hi,
Attached is a brief request from Dr. Solomon at NEJM. Let me know if you have specific comments. I can send it to her before the week is out!!
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20592
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Dear Dr. Solomon

The NICHD NRN has recently completed a large multicenter SUPPORT Trial (SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants) with over 1300 infants enrolled into the study.

This prospective, randomized, factorial 2X2 design trial had two main hypotheses:
1). Relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a ~~permissive~~ protocol defined ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.
2). Relative to infants managed with a higher more conventional SpO2 range (91% to 95%) ~~SpO2 range~~ that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

~~This is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors tested are:~~
~~1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (< 1 hour) surfactant and mechanical ventilation.~~
~~2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.~~

We have two separate papers focusing on the two separate arms of the factorial design ~~, each of which addresses on of the two primary outcomes from the two original hypotheses (ventilation strategy and oximetry)~~ addressing each of the two hypotheses above. We intend to submit both papers to the NEJM. ~~Are~~ Please let me know if there are any special guidelines for reporting studies with factorial designs set forth by NEJM~~.~~? Your assistance is appreciated in advance.

Best regards,

Rosemary D. Higgins, MD on behalf of the NICHD Neonatal Research Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:20:41 PM

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 12:05:45 2009
Subject: RE: Request for conflict of interest information for NEJM

No

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 11:45 AM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; mcw3@cwru.edu; Wade RIch; Gantz, Marie; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Das, Abhik; Poole, W. Kenneth; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:20:12 PM

From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 12:15:57 2009
Subject: Re: Request for conflict of interest information for NEJM

No conflict of interest.
Dale L. Phelps

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; Wade RIch <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Roger Faix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; Abhik Das (adas@rti.org) <adas@rti.org>; poo@rti.org <poo@rti.org>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Nancy Newman <nxs5@cwru.edu>; IFrantz@tufts-nemc.org <IFrantz@tufts-nemc.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; anthony_piazza@oz.ped.emory.edu <anthony_piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama; Phelps, Dale; bpoindex@iupui.edu <bpoindex@iupui.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; vanmeurs@stanford.edu <vanmeurs@stanford.edu>; sduara@miami.edu <sduara@miami.edu>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Sood, Beena [bsood@med.wayne.edu] <bsood@med.wayne.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Ed Bell (edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu) <kwatterberg@salud.unm.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Cc: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>
Sent: Tue Nov 17 11:44:48 2009
Subject: Request for conflict of interest information for NEJM

Hi,
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Abhik Das (adas@rti.org); Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for Dr. Solomon NEJM
Date: Tuesday, November 17, 2009 12:18:53 PM
Attachments: Dr. Solomon inquiry.doc

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Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:06:58 PM

----- Original Message -----
From: Edward Bell <edward-bell@uiowa.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 12:02:14 2009
Subject: Re: Request for conflict of interest information for NEJM

I have no conflicts for either paper.

Sent from my phone

-----Original Message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Date: Tue, 17 Nov 2009 11:44:48
To: wcarlo@peds.uab.edu<wcarlo@peds.uab.edu>; nfiner@ucsd.edu<nfiner@ucsd.edu>; mcw3@cwru.edu<mcw3@cwru.edu>; Wade RIch<wrich@ucsd.edu>; mgantz@rti.org<mgantz@rti.org>; alaptook@WIHRI.org<alaptook@WIHRI.org>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Roger Faix (Roger.Faix@hsc.utah.edu)<Roger.Faix@hsc.utah.edu>; Abhik Das (adas@rti.org)<adas@rti.org>; poo@rti.org<poo@rti.org>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Nancy Newman<nxs5@cwru.edu>; IFrantz@tufts-nemc.org<IFrantz@tufts-nemc.org>; Pablo.Sanchez@UTSouthwestern.edu<Pablo.Sanchez@UTSouthwestern.edu>; anthony_piazza@oz.ped.emory.edu<anthony_piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama<Nirupama_Laroia@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu<dale_phelps@URMC.Rochester.edu>; bpoindex@iupui.edu<bpoindex@iupui.edu>; cotte010@mc.duke.edu<cotte010@mc.duke.edu>; vanmeurs@stanford.edu<vanmeurs@stanford.edu>; sduara@miami.edu<sduara@miami.edu>; (Vivek.Narendran@cchmc.org)<Vivek.Narendran@cchmc.org>; Sood, Beena[bsood@med.wayne.edu] <bsood@med.wayne.edu>; moshea@wfubmc.edu<moshea@wfubmc.edu>; Ed Bell (edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; richard.ehrenkranz@yale.edu<richard.ehrenkranz@yale.edu>; Kristi Watterberg(kwatterberg@salud.unm.edu)<kwatterberg@salud.unm.edu>; Higgins, Rosemary(NIH/NICHD) [E] <higginsr@mail.nih.gov>
Cc: Archer, Stephanie (NIH/NICHD) [E]<archerst@mail.nih.gov>
Subject: Request for conflict of interest information for NEJM

Hi,
You are an author on the SUPPORT OXIMETRY Paper. I need to know if you have any conflict with the publication of this manuscript. Please respond to me with a yes (including specific conflicts) or no by November 19.

Thanks
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:02:40 PM

----- Original Message -----
From: Duara, Shahnaz <SDuara@med.miami.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 11:56:04 2009
Subject: Re: Request for conflict of interest information for NEJM

I have no conflict.
Shahnaz

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; Wade RIch <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Roger Faix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; Abhik Das (adas@rti.org) <adas@rti.org>; poo@rti.org <poo@rti.org>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Nancy Newman <nxs5@cwru.edu>; IFrantz@tufts-nemc.org <IFrantz@tufts-nemc.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; anthony_piazza@oz.ped.emory.edu <anthony_piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama <Nirupama_Laroia@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@urmc.rochester.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; vanmeurs@stanford.edu <vanmeurs@stanford.edu>; sduara@miami.edu <sduara@miami.edu>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Sood, Beena [bsood@med.wayne.edu] <bsood@med.wayne.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Ed Bell (edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu) <kwatterberg@salud.unm.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Cc: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>
Sent: Tue Nov 17 11:44:48 2009
Subject: Request for conflict of interest information for NEJM

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 12:01:46 PM

----- Original Message -----
From: Rich, Wade <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 17 11:56:04 2009
Subject: RE: Request for conflict of interest information for NEJM

No.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 17, 2009 8:45 AM
To: wcarlo@peds.uab.edu; Finer, Neil; mcw3@cwru.edu; Rich, Wade; mgantz@rti.org; alaptook@WIHRI.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; Nancy Newman; IFrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; anthony_piazza@oz.ped.emory.edu; (b) (6) Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@miami.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Importance: High

Hi,
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Request for conflict of interest information for NEJM
Date: Tuesday, November 17, 2009 11:44:48 AM
Attachments: Boilerplate, Carlo, SUPPORT Oximetry, 2009-11-16 author table[1].doc
Importance: High

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Thanks
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SUPPORT Oximetry (without FU)

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From: Ronald N Goldberg
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: ***Confidential FW: CPAP - Surf Manuscript
Date: Tuesday, November 17, 2009 8:32:06 AM
Attachments: SUPPORT NEJM Nov16 final.doc

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11/16/2009 04:14 PM

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cc

Subject ***Confidential FW: CPAP - Surf Manuscript

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 16, 2009 2:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Abhik Das; Gantz, Marie

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Hi Rose
Here is our "Final" incorporating all changes that we agree with as of 5 minutes ago.
Please circulate and lets discuss this version
Many thanks
Neil
[attachment "NEJM Tables Nov 10.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke] [attachment "SUPPORT NEJM Nov16 final.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT, CCRC[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler[8]; Edward Donovan[8]; Vivek Narendran, MD MRCP[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Vineet Bhandari, MD, DM[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/~~7~~7~~ths~~ ~~weeks~~ to 27 6/7~~ths~~ weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of two~~2~~ ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was not~~non~~-significantly reduced in the CPAP ~~group~~ compared to the surfactant group, (48.7% vs. 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs. 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

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Conclusions: CPAP as used in this study is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD nor neurodevelopmental outcome, but may do so for the most immature infants ~~and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI)~~.[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent trial by Morley et al randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had ~~evidence of~~ respiratory distress ~~at that time~~. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. ~~CPAP infants were intubated if they met failure criteria.~~[10] This study did not compare early CPAP to the early administration of surfactant which ~~, and surfactant use~~ followed unit protocol~~standard of care~~. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with ~~the findings of~~ an earlier meta analysis**Error! Bookmark not defined.**[4]. A reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

Comment [rng1]: Sentence fragment

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The primary outcome of death or BPD at 36 weeks ~~was showed non-~~ was notsignificantly reduced in the CPAP arm, (33.9% vs 38.9%, (OR=0.58 to 1.12; P=0.19).

The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately. The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, use of early CPAP and a protocol driven strategy of limited ventilation in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in ~~an~~ increased survival without BPD at 36 weeks.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen.

Eligible infants were 24 0/7t~~hs~~ to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to

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provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7~~ths~~ to 25 6/7~~ths~~ ~~weeks,~~ and 26 0/7~~ths~~-27 6/7~~ths~~ weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 <0 .50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant

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patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After three~~3~~ intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq 0.35$ with a $SpO_2 \geq 88\%$, a MAP < 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition

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after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the two~~2~~ factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for gendersex, birth weight, or race between the two 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend(p=) for higher DR mortality which was not statistically significant. In the delivery room, surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants(, $p<0.001$), Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata~~,~~ (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034), Tables 3 and 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

Comment [rng2]: Seems redundant.see above

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but two ~~2~~ infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, (20.5% vs. 13.0%, p=0.023) for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups(, 10.8% vs 10.2%). The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported trial of Morley et al[10-15] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention. We also included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

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We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without

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neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Comment [rng3]: Reference physiologic definition

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7~~ths~~ weeks gestation assigned to treatment with CPAP as used in this trial have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most

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immature infants. CPAP as used in this trial is an effective evidence-based alternative to intubation and surfactant for very preterm infants.

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From:	Brenda Morris
To:	Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; wcarlo@peds.uab.edu; Kathleen A Kennedy; Jon E Tyson; nfiner@ucsd.edu
Subject:	More comments
Date:	Monday, November 16, 2009 5:10:40 PM
Attachments:	SUPPORT NEJM Nov12 Final.morris.doc

Dear Neil, I read through the manuscript and thoroughly enjoyed seeing all of your hard work come to fruition. Congrats!!!!!! I have the advantage or disadvantage of having not seen this data before and of having not heard y'all talk about it before. So, I sort of consider my comments "fresh eyes".... someone who knows the protocol but hasn't dealt with it in awhile. I think my main comment would be that I would change the "surfactant" group name to "Early Intubation" or "Intubation" (to save words) or something like that. As I read the manuscript.... it seems like you are putting down the use of surfactant.... but what you are really trying to say is that it isn't beneficial to intubate these kids early... but if you do finally intubate them then give surfactant. By changing the group name I think you will avoid this impression. I also found some typos and other details. I had a few suggestions about how to reword things to make it clearer.

I had received an invitation to the call this afternoon and listened in for awhile, but needed to get off to see babies. I would agree that the NEJM will not allow you to include the strata stuff in the abstract. They also won't let you use ANY abbreviations. Thanks for the opportunity to review. I will try and look at Wally's manuscript as well. Sincerely, Brenda Morris

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

NEIL, do you want to call them the Surfactant group or the "Early Intubation group (EI)"???? Looks like you are picking on surfactant when surfactant may be beneficial, but the intubation and ventilation is probably the culprit???? Was the decrease in deaths due to better survival in the babies who were not intubated??? I would assume this, but it might help your conclusion to be able to show that.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 ??? ok to use abbreviation without spelling it out previously???? while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

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Conclusions: The use of CPAP is an effective evidence based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant~~, and~~ as the surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis[4] ???REFERENCE????, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks.

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Infants were also randomized to a prospective comparison using purpose altered oximeters of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen. ~~using purpose-altered oximeters.~~

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~~The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.~~

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a ~~randomizing~~ participating center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm – NEIL, As a person who knows about this trial but hasn't seen any of the results or been in on a discussion recently..... I had a hard time deciphering this paragraph. It wasn't clear that you were providing CPAP preferentially. I rearranged the sentences a bit. Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP +5 as soon as possible after birth. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR. Intubation was to be performed only for the standard NRP indications.[11] CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. ~~CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required~~

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~~intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.~~[12]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life the infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable~~, and~~ without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were subsequently extubated ~~treated~~ using NICU specific standard practice. You could also say, "After 2 failed extubations, CPAP infants were subsequently extubated using center specific standard practice."

~~**Surfactant**~~ **Early Intubation Arm**: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, aAn FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and

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hemodynamically stable without evidence of clinically significant PDA. ~~Once extubated~~ ~~Surfactant~~Early intubation infants were treated using NICU standard practice after extubation.

For both groups intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. ~~For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.~~

~~Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.~~

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline ~~occurrence~~ data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment group as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition ~~after discharge and before follow-up~~prior to follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

Neil, This paragraph really didn't make much sense. Attempted to rework it. There was a prospective decision to also evaluate the occurrence of BPD using the "~~P~~physiologic

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d~~D~~efinition" as defined by Walsh, et al (REFERNCE) as ~~which assigned the diagnosis of BPD to~~ any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, ~~but~~ or failed~~required demonstration of oxygen dependence by~~ an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1314]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering (is this due to twins???). A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results~~, including those concerning adverse outcomes,~~ four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

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The study was approved by Human Subjects Committees at all sites and RTI International, the NRN data center. Parental consent for participation in the trial was required before deliveryenrollment. (You could actually enroll them after delivery!)

Results:

There were 1,316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant Early Intubation group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant, was given to 14.1% of the CPAP versus 51.4% of the surfactant early intubation group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2. How many of the CPAP infants never required intubation? I don't think you ever state this.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant early intubation group, 48.7% versus 54.1%, (RR 0.91, 05% CI 0.83, 1.01, p=0.072)

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when adjusted for gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034), Table 4. Overall, there was a non-significant reduction in the occurrence of BPD at 36 weeks based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm,(RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity ~~using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group~~[15] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Neil, It looks like the days of mechanical ventilation is based only on the babies who were intubated. Shouldn't it be based on all babies randomized to the group????? That should show a much shorter duration in the CPAP group.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP intitiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in

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the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[16] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[17]

Our trial differs from the recently reported COIN trial[10~~10~~~~15~~] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as ~~units~~ practitioners currently using early CPAP tend to have a higher threshold for intubation.

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We prospectively identified safety outcomes that we chose to follow as investigators. These included; the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to ~~the use of early surfactant~~early intubation and surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months. ~~and t~~These results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids, and a reduction in BPD in the overall CPAP group ~~without any increase in adverse neonatal outcomes~~ represents a substantial clinical benefit compared with ~~the initial use of early surfactant~~early intubation and surfactant therapy.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment

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with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of early CPAP in such infants is an effective ~~evidence-based~~ alternative to intubation and surfactant.

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From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Abhik Das; Gantz, Marie
Subject:	CPAP - Surf Manuscript
Date:	Monday, November 16, 2009 2:45:09 PM
Attachments:	NEJM Tables Nov 10.doc SUPPORT NEJM Nov16 final.doc

Hi Rose
Here is our "Final" incorporating all changes that we agree with as of 5 minutes ago.
Please circulate and lets discuss this version
Many thanks
Neil

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)	0.9686
	26-27	57.0% (378/663)	57.1% (373/653)	
Male		51.6% (342/663	56.7% (370/653	0.0646
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)	0.3681
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)	
	Hispanic	20.8% (138/663)	18.5% (121/653)	
	Other/unknown	3.2% (21/663)	4.0% (26/653)	
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Antenatal steroids (any)		96.8% (642/663	95.6% (623/652	0.2248
Antenatal steroids (full course)		73.6% (486/660	69.8% (453/649	0.1232
Death in the DR (per SUPP03/SUPP04)		0.2% (1/663)	0.8% (5/653)	0.0978

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661	25.6% (167/653	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662	92.9% (606/652	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663	22.4% (146/653	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660	93.4% (609/652	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660	27.0% (176/652	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67.1% (443/660	98.9% (646/653	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Death at any time while hospitalized	16.4% (109/663	19.6% (128/653	0.84 (0.67, 1.05)	0.1259
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
Discharge on oxygen	22.2% (122/550	23.9% (124/519	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655	48.8% (318/652	1.14 (1.03, 1.25)	0.0111
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. Outcomes for 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Total LOS any hospital* Mean±StdErr (N=407)	122.0 ± 2.9	119.0 ± 3.1		0.4690
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 5. Cause of Death - 24-25 week Strata

Variable	Category	CPAP (N=68)	Surfactant (N=90)	Unadjusted P-value
Contributory cause of death	1=RDS	13/68 (19.1)	31/90 (34.4)	0.1212
	2=BPD	10/68 (14.7)	7/90 (7.8)	
	3=Infection	14/68 (20.6)	15/90 (16.7)	
	4=NEC	10/68 (14.7)	16/90 (17.8)	
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)	
	6=Immaturity	3/68 (4.4)	5/90 (5.6)	
	7=Other	7/68 (10.3)	11/90 (12.2)	

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs. 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs. 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

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Conclusions: The use of CPAP is an effective evidence-based alternative to intubation and surfactant in preterm infants.

Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis**Error! Bookmark not defined.**. A reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). The primary outcome of death or BPD at 36 weeks showed a non-significant difference.

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a protocol driven strategy of limited ventilation in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were

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randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant

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patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30, $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a MAP < 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data (BPD 67%, NDI 61%). We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition

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after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant, was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, $p=0.072$) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Gantz, Marie
To: Finer, Neil; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: CPAP vs SURF
Date: Monday, November 16, 2009 2:10:18 PM

The p-values in Table 1 looking at whether randomization resulted in balance between treatments in terms of demographics are unadjusted because we are not looking at outcomes. However, if we think it makes more sense to make them adjusted I can do that.

All p-values for primary and secondary outcomes are adjusted. The only other unadjusted p-value is in the COD table. If we need an adjusted p-value I can produce one.

The reason that standard errors are presented instead of standard deviations in the tables with the adjusted tests is that the means in that table are adjusted for covariates. Standard errors give an estimate of how sure we are of our estimate of the adjusted mean. Another way we could go is to present CIs for the adjusted means.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 16, 2009 1:59 PM
To: Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: CPAP vs SURF

Hi Marie
I had asked some of these questions earlier -
Why do we use unadjusted and adjusted p values. I assume that we would use adjusted for all primary and secondaries and unadjusted for the others - Is this what you have done??
Why do we flip between SD for gestation and birth weight and SEM for others??
Thanks
Neil
------ Forwarded Message
From: Wade Rich <wrich@ucsd.edu>
Date: Mon, 16 Nov 2009 08:52:02 -0800
To: Neil Finer <nfiner@ucsd.edu>
Subject: FW: CPAP vs SURF

Here is what I have done and not done from Seetha's comments. You may want to do more.
wade

Abstract:
a) I suggest expand SUPPORT in Methods Section and BPD in Results

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section. BPD already Done. SUPPORT not done
b) could you add how many of the infants in CPAP group subsequently required surfactant? I believe data is in Table 1. Also, was outcome know for all infants? In the abstract?
c) If you are tight for space in abstract, I suggest leave out "familial clustering" in Results and "evidence based" in the Conclusion No Need.

Introduction:
a) please clarify the primary outcome of COIN trial for ease for the NEJM reader Please look at this sentence
b) I would move the SUPPORT study hypothesis to the end of the Introduction, before Methods

Methods
a) I suggest you take out the "purpose altered oximeters" and just say there was the oximeters arm--as you have done later. Why open a Pandora's box?
I agree, but did not do this.
b) Substitute "NRN center" rather than "randomizing center" Not done
c) Under sample size---can you please provide the anticipated event rate in the early CPAP arm? We took these out for space a while ago for space, just saying we used 2000 baseline data.
d) can you clarify what the primary outcome is here (in abstract it says death or BPD, while here it appears to be death or disability--to me death or disability was a secondary outcome). Seems clear to me.
e) How was attrition rate of 17% arrived at---I think it is average loss to follow up in our FU studies---maybe you can state that? We asked Ken !
d) Is PHY BPD a secondary outcome? I wonder if you can make the description of PHY BPD definition a little clearer---maybe "step-wise oxygen-reduction to room air challenge among infants requiring > 30% oxygen without an assistance in ventilation" or some such wording. This came from Fanaroff.
e) expand PMA and clarify data center at RTI International, Research Triangle Park, NC and DSMC in caps If RTI did not ask to expand it, I would not take the space.

Results
a) for the CPAP paper do you really need to say Enrollment was halted for oxygen arm etc etc? I suggest leaving it out Your call.
b) Table 1: were any other maternal variables evaluated---mode of delivery, hypertension/PET? This is a study that might be influenced by perinatal variables other than ANCS. I suggest GA be shown in completed weeks and P values to 2 decimal points only in all Tables.
c) Table 2: I am not sure I follow why unadjusted P values are given for demographic (Table 1) but adjusted for Table 2.
d) Delivery room variables, Table 4 is cited in the Results section before Table 3---maybe you can change the Table order?
e) Table 3: Why was SEM used here rather than SD? Also, suggest expand Medical and surgical NEC. PDA, IVH--preferably ICH, in footnote
f) Since the study involved 24 to 28 wk infants, why show only lower strata in Table 4????
g) Is Table 5 necessary? Again, why is P value here unadjusted?
h) Was center not a variable for adjustment or did I miss something? I am not doing anything to the tables without direct consultation.

Discussion

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a) I am not sure I understand "higher threshold approach for intubation" Can this be clarified? I took out 'approach'.
b) can you speculate why the overall outcome was not different in the 2 groups
c) Should any weaknesses be mentioned--

I know you are restrained by word count, but I believe expanding the discussion might help

Hope this helps
All the best
Seetha

------ End of Forwarded Message

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Blansfield, Earl (NIH/NICHD) [E]

From: Walsh, Michele <Michele.Walsh@UHhospitals.org>
Sent: Monday, November 16, 2009 1:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Great talk to you this afternoon.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 1:38 PM
To: Walsh, Michele
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Thanks for the heads up!

DSMC wants the death information shared with the other DSMCs. This is in progress.

Rose

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, November 16, 2009 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

No but I can.
Also: we have an issue: junior colleague of Neil Was speaking about SUPPORT results at another meeting Quite openly.
We spoke to Neil, and he said he would Take care of it. Don't know if we need to do more?
Also: was there any issue from DSMC? I was waiting to hear Before sharing with our faculty.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 11:31 AM
To: Walsh, Michele
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

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Did you send back to Neil?

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, November 16, 2009 11:30 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

A couple of suggestions highlighted In turquoise.
Biggest: I do not believe that NEJM will allow statements Like non significant reduction in BPD: it is Not different. Steering committee was very clear about this Yet the language remains.

Michele Walsh
beeper(b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 14, 2009 2:39 AM
To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu'; 'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu';
(b) (6) 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; 'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu'; 'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu'; 'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'moshea@wfubmc.edu'; 'mcaplan@northshore.org'; 'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu'; 'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org'; 'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-
Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 17:06:37 2009
Subject: CPAP vs SURF

Wally and Rose

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Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were opposite so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
Neil

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Blansfield, Earl (NIH/NICHD) [E]

From: Walsh, Michele <Michele.Walsh@UHhospitals.org>
Sent: Monday, November 16, 2009 1:39 PM
To: Neil_Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Attachments: SUPPORT NEJM Nov12 Final VB plus MW comments.doc

Hi Neil: I just added a couple of edits to what Vaneeti
Suggested. My main concern is that I think you should say
BPD was not different as opposed to reduced but not statistically significant.
Talk to you soon.

Michele Walsh
Medical Director NICU
Rainbow Babies & Childrens Hospital
Case Medical Center
Professor, Deparment of Pediatrics
Case Western Reserve University
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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Vivek Narendran, MD MRCP[8]; Edward Donovan[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; ~~Richard A. Ehrenkranz, MD~~ Vineet Bhandari, MD, DM[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

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Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Abstract: 246

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Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 ~~min~~ minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP -is an effective **evidence--based** alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 -to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] In [redacted] surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta-analysis**Error! Bookmark not defined.**[7] ~~and a~~ A **reduction in** death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks was also noted in that study.

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their

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exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, ~~that~~ the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, ~~AAnn~~ $FiO_2 \leq .35$ with a $SpO_2 \geq 88\%$, a ~~mean airway pressure (~~MAP~~)~~ < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on ~~high frequency ventilation (~~HFV~~)~~, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after

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discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [12,13]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, [redacted] of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (-RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

Comment [mw1]: Is this backwards? Control grp (surfactant is 44.3% which was lower in the CPAP 40.2%.
I do not think that you can say it was reduced: I think you can say it was the same.
Have we also looked at 40 wks? Ballard's group has found that 40 wks may be more predictive.

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for [redacted] compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

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The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

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Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Finer, Neil
To: Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Subject: Re: CPAP vs SURF
Date: Monday, November 16, 2009 2:38:48 PM
Attachments: NEJM Tables Nov 10.doc

Thanks Marie
Can you quickly provide the adjusted values for the Death Table (Table 5). I would leave the rest and use your explanation if queried
Thanks
Neil

On 11/16/09 11:10 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

> The p-values in Table 1 looking at whether randomization resulted in
> balance between treatments in terms of demographics are unadjusted
> because we are not looking at outcomes. However, if we think it makes
> more sense to make them adjusted I can do that.
>
> All p-values for primary and secondary outcomes are adjusted. The only
> other unadjusted p-value is in the COD table. If we need an adjusted
> p-value I can produce one.
>
> The reason that standard errors are presented instead of standard
> deviations in the tables with the adjusted tests is that the means in
> that table are adjusted for covariates. Standard errors give an estimate
> of how sure we are of our estimate of the adjusted mean. Another way we
> could go is to present CIs for the adjusted means.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Monday, November 16, 2009 1:59 PM
> To: Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Das,
> Abhik
> Subject: FW: CPAP vs SURF
>
> Hi Marie
> I had asked some of these questions earlier -
> Why do we use unadjusted and adjusted p values. I assume that we would
> use adjusted for all primary and secondaries and unadjusted for the
> others - Is this what you have done??
> Why do we flip between SD for gestation and birth weight and SEM for
> others??
> Thanks
> Neil
> ------ Forwarded Message
> From: Wade Rich <wrich@ucsd.edu>

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> Date: Mon, 16 Nov 2009 08:52:02 -0800
> To: Neil Finer <nfiner@ucsd.edu>
> Subject: FW: CPAP vs SURF
>
> Here is what I have done and not done from Seetha's comments. You may
> want to do more.
> wade
>
> Abstract:
> a) I suggest expand SUPPORT in Methods Section and BPD in Results
> section. BPD already Done. SUPPORT not done
> b) could you add how many of the infants in CPAP group subsequently
> required surfactant? I believe data is in Table 1. Also, was outcome
> know for all infants? In the abstract?
> c) If you are tight for space in abstract, I suggest leave out "familial
> clustering" in Results and "evidence based" in the Conclusion No Need.
>
> Introduction:
> a) please clarify the primary outcome of COIN trial for ease for the
> NEJM reader Please look at this sentence
> b) I would move the SUPPORT study hypothesis to the end of the
> Introduction, before Methods
>
> Methods
> a) I suggest you take out the "purpose altered oximeters" and just say
> there was the oximeters arm--as you have done later. Why open a
> Pandora's box?
> I agree, but did not do this.
> b) Substitute "NRN center" rather than "randomizing center" Not done
> c) Under sample size---can you please provide the anticipated event rate
> in the early CPAP arm? We took these out for space a while ago for
> space, just saying we used 2000 baseline data.
> d) can you clarify what the primary outcome is here (in abstract it says
> death or BPD, while here it appears to be death or disability--to me
> death or disability was a secondary outcome). Seems clear to me.
> e) How was attrition rate of 17% arrived at---I think it is average loss
> to follow up in our FU studies---maybe you can state that? We asked Ken
> !
> d) Is PHY BPD a secondary outcome? I wonder if you can make the
> description of PHY BPD definition a little clearer---maybe "step-wise
> oxygen-reduction to room air challenge among infants requiring > 30%
> oxygen without an assistance in ventilation" or some such wording. This
> came from Fanaroff.
> e) expand PMA and clarify data center at RTI International, Research
> Triangle Park, NC and DSMC in caps If RTI did not ask to expand it, I
> would not take the space.
>
> Results
> a) for the CPAP paper do you really need to say Enrollment was halted
> for oxygen arm etc etc? I suggest leaving it out Your call.
> b) Table 1: were any other maternal variables evaluated---mode of
> delivery, hypertension/PET? This is a study that might be influenced by
> perinatal variables other than ANCS. I suggest GA be shown in completed
> weeks and P values to 2 decimal points only in all Tables.
> c) Table 2: I am not sure I follow why unadjusted P values are given for
> demographic (Table 1) but adjusted for Table 2.
> d) Delivery room variables, Table 4 is cited in the Results section

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> before Table 3---maybe you can change the Table order?
> e) Table 3: Why was SEM used here rather than SD? Also, suggest expand
> Medical and surgical NEC. PDA, IVH--preferably ICH, in footnote
> f) Since the study involved 24 to 28 wk infants, why show only lower
> strata in Table 4????
> g) Is Table 5 necessary? Again, why is P value here unadjusted?
> h) Was center not a variable for adjustment or did I miss something? I
> am not doing anything to the tables without direct consultation.
>
> Discussion
> a) I am not sure I understand "higher threshold approach for intubation"
> Can this be clarified? I took out 'approach'.
> b) can you speculate why the overall outcome was not different in the 2
> groups
> c) Should any weaknesses be mentioned--
>
> I know you are restrained by word count, but I believe expanding the
> discussion might help
>
> Hope this helps
> All the best
> Seetha
>
>
> ------ End of Forwarded Message

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)	0.9686
	26-27	57.0% (378/663)	57.1% (373/653)	
Male		51.6% (342/663	56.7% (370/653	0.0646
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)	0.3681
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)	
	Hispanic	20.8% (138/663)	18.5% (121/653)	
	Other/unknown	3.2% (21/663)	4.0% (26/653)	
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Antenatal steroids (any)		96.8% (642/663	95.6% (623/652	0.2248
Antenatal steroids (full course)		73.6% (486/660	69.8% (453/649	0.1232
Death in the DR (per SUPP03/SUPP04)		0.2% (1/663)	0.8% (5/653)	0.0978

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661	25.6% (167/653	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662	92.9% (606/652	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663	22.4% (146/653	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660	93.4% (609/652	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660	27.0% (176/652	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67.1% (443/660	98.9% (646/653	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Death at any time while hospitalized	16.4% (109/663	19.6% (128/653	0.84 (0.67, 1.05)	0.1259
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
Discharge on oxygen	22.2% (122/550	23.9% (124/519	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655	48.8% (318/652	1.14 (1.03, 1.25)	0.0111
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. Outcomes for 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Total LOS any hospital* Mean±StdErr (N=407)	122.0 ± 2.9	119.0 ± 3.1		0.4690
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 5. Cause of Death - 24-25 week Strata

Variable	Category	CPAP (N=68)	Surfactant (N=90)	Unadjusted P-value
Contributory cause of death	1=RDS	13/68 (19.1)	31/90 (34.4)	0.1212
	2=BPD	10/68 (14.7)	7/90 (7.8)	
	3=Infection	14/68 (20.6)	15/90 (16.7)	
	4=NEC	10/68 (14.7)	16/90 (17.8)	
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)	
	6=Immaturity	3/68 (4.4)	5/90 (5.6)	
	7=Other	7/68 (10.3)	11/90 (12.2)	

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From: Finer, Neil
To: Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: CPAP vs SURF
Date: Monday, November 16, 2009 2:02:06 PM

Hi Seetha
Many thanks for your detailed review. We will incorporate many of these that have not already been done. I will remove the mention of stopping, and the purpose built oximeters
Center was a variable for adjustment, many asked for the cause of death including another internal reviewer
We will try to get these al changed and the submit and let the reviewers have a say.
Thanks again
Neil

On 11/16/09 7:58 AM, "Shankaran, Seetha" <sshankar@med.wayne.edu> wrote:

> Hi Neil
> Great to see you last week. Rose had asked me to be an "internal reviewer" for
> this paper. I will not be able to be on the conf call today (on my way to MLS
> PI meeting).
> I congratulate you getting the paper written so well and so quickly. I have a
> few comments and am basing them on my experience with NEJM and Hypothermia RCT
> paper. Remember, when they are done with you, you won't recognize your
> paper---just kidding!
>
> Abstract:
> a) I suggest expand SUPPORT in Methods Section and BPD in Results section.
> b) could you add how many of the infants in CPAP group subsequently required
> surfactant? I believe data is in Table 1. Also, was outcome know for all
> infants?
> c) If you are tight for space in abstract, I suggest leave out "familial
> clustering" in Results and "evidence based" in the Conclusion
>
> Introduction:
> a) Expand COIN and maybe substitute "clinical center" for "unit"? also, please
> clarify the primary outcome of COIN trial for ease for the NEJM reader
> b) I would move the SUPPORT study hypothesis to the end of the Introduction,
> before Methods
>
> Methods
> a) I suggest you take out the "purpose altered oximeters" and just say there
> was the oximeters arm--as you have done later. Why open a Pandora's box?
> b) Substitute "NRN center" rather than "randomizing center"
> c) Under sample size---can you please provide the anticipated event rate in
> the early CPAP arm?
> d) can you clarify what the primary outcome is here (in abstract it says death
> or BPD, while here it appears to be death or disability--to me death or
> disability was a secondary outcome).
> e) How was attrition rate of 17% arrived at---I think it is average loss to
> follow up in our FU studies---maybe you can state that?
> d) Is PHY BPD a secondary outcome? I wonder if you can make the description of
> PHY BPD definition a little clearer---maybe "step-wise oxygen-reduction to

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> room air challenge among infants requiring > 30% oxygen without an assistance
> in ventilation" or some such wording.
> e) expand PMA and clarify data center at RTI International, Research Triangle
> Park, NC and DSMC in caps
>
> Results
> a) for the CPAP paper do you really need to say Enrollment was halted for
> oxygen arm etc etc? I suggest leaving it out
> b) Table 1: were any other maternal variables evaluated---mode of delivery,
> hypertension/PET? This is a study that might be influenced by perinatal
> variables other than ANCS. I suggest GA be shown in completed weeks and P
> values to 2 decimal points only in all Tables.
> c) Table 2: I am not sure I follow why unadjusted P values are given for
> demographic (Table 1) but adjusted for Table 2.
> d) Delivery room variables, Table 4 is cited in the Results section before
> Table 3---maybe you can change the Table order?
> e) Table 3: Why was SEM used here rather than SD? Also, suggest expand Medical
> and surgical NEC. PDA, IVH--preferably ICH, in footnote
> f) Since the study involved 24 to 28 wk infants, why show only lower strata in
> Table 4????
> g) Is Table 5 necessary? Again, why is P value here unadjusted?
> h) Was center not a variable for adjustment or did I miss something?
>
> Discussion
> a) I am not sure I understand "higher threshold approach for intubation" Can
> this be clarified?
> b) can you speculate why the overall outcome was not different in the 2 groups
> c) Should any weaknesses be mentioned--
>
> I know you are restrained by word count, but I believe expanding the
> discussion might help
>
> Hope this helps
> All the best
> Seetha
>
> _____
> From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
> Sent: Saturday, November 14, 2009 2:38 AM
> To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; Shankaran, Seetha;
> Sood, Beena; 'susie.buchter@oz.ped.emory.edu';
> 'Anthony.Piazza@oz.ped.emory.edu'; (b) (6)
> 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org'; 'Vivek.Narendran@cchmc.org';
> 'vineet.bhandari@yale.edu'; 'edward.donovan@cchmc.org';
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> 'Bradley.yoder@hsc.utah.edu'; 'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
> Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org';
> 'mcunningham@rti.org'; 'petrie@rti.org'
> Subject: ++++CONFIDENTIAL: CPAP vs SURF
>

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> Hi-
> Here is the most recent draft of the CPAP/surfactant paper.
>
> We will discuss on Monday's call.
>
> Thanks for all the assistance
>
>
> Rose
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E];
> Rich, Wade <wrich@ucsd.edu>
> Sent: Thu Nov 12 17:06:37 2009
> Subject: CPAP vs SURF
>
> Wally and Rose
> Here is the "final" CPAP vs Surf paper
> It fits NEJM and incorporates all suggestions although some were opposite so
> we made some choices.
> Please review
> Wally can you make sure our definitions for BPD etc are identical??
> Thanks
> I would like to get these submitted
> Please share with me your thoughts
> Be well
> Neil
>

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From: Finer, Neil
To: Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Subject: FW: CPAP vs SURF
Date: Monday, November 16, 2009 1:56:34 PM
Attachments: SUPPORT NEJM Nov16_0850wr.doc

Hi Marie
I had asked some of these questions earlier -
Why do we use unadjusted and adjusted p values. I assume that we would use adjusted for all primary and secondaries and unadjusted for the others – Is this what you have done??
Why do we flip between SD for gestation and birth weight and SEM for others??
Thanks
Neil
------ Forwarded Message
From: Wade Rich <wrich@ucsd.edu>
Date: Mon, 16 Nov 2009 08:52:02 -0800
To: Neil Finer <nfiner@ucsd.edu>
Subject: FW: CPAP vs SURF

Here is what I have done and not done from Seetha's comments. You may want to do more.
wade

Abstract:
a) I suggest expand SUPPORT in Methods Section and BPD in Results section. BPD already Done. SUPPORT not done
b) could you add how many of the infants in CPAP group subsequently required surfactant? I believe data is in Table 1. Also, was outcome know for all infants? In the abstract?
c) If you are tight for space in abstract, I suggest leave out "familial clustering" in Results and "evidence based" in the Conclusion No Need.

Introduction:
a) please clarify the primary outcome of COIN trial for ease for the NEJM reader Please look at this sentence
b) I would move the SUPPORT study hypothesis to the end of the Introduction, before Methods

Methods
a) I suggest you take out the "purpose altered oximeters" and just say there was the oximeters arm--as you have done later. Why open a Pandora's box?
I agree, but did not do this.
b) Substitute "NRN center" rather than "randomizing center" Not done
c) Under sample size---can you please provide the anticipated event rate in the early CPAP arm? We took these out for space a while ago for space, just saying we used 2000 baseline data.
d) can you clarify what the primary outcome is here (in abstract it says death or BPD, while here it appears to be death or disability--to me death or disability was a secondary outcome). Seems clear to me.
e) How was attrition rate of 17% arrived at---I think it is average loss to follow up in our FU studies---maybe you can state that? We asked Ken !
d) Is PHY BPD a secondary outcome? I wonder if you can make the description of PHY BPD definition a little clearer---maybe "step-wise oxygen-reduction to room air challenge among infants requiring > 30% oxygen without an assistance in ventilation" or some such wording. This came from Fanaroff.
e) expand PMA and clarify data center at RTI International, Research Triangle Park, NC and DSMC in caps If RTI did not ask to expand it, I would not take the space.

Results
a) for the CPAP paper do you really need to say Enrollment was halted for oxygen arm etc etc? I suggest leaving it out Your call.
b) Table 1: were any other maternal variables evaluated---mode of delivery, hypertension/PET? This is a study that

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might be influenced by perinatal variables other than ANCS. I suggest GA be shown in completed weeks and P values to 2 decimal points only in all Tables.
c) Table 2: I am not sure I follow why unadjusted P values are given for demographic (Table 1) but adjusted for Table 2.
d) Delivery room variables, Table 4 is cited in the Results section before Table 3---maybe you can change the Table order?
e) Table 3: Why was SEM used here rather than SD? Also, suggest expand Medical and surgical NEC. PDA, IVH--preferably ICH, in footnote
f) Since the study involved 24 to 28 wk infants, why show only lower strata in Table 4????
g) Is Table 5 necessary? Again, why is P value here unadjusted?
h) Was center not a variable for adjustment or did I miss something? I am not doing anything to the tables without direct consultation.

Discussion
a) I am not sure I understand "higher threshold approach for intubation" Can this be clarified? I took out 'approach'.
b) can you speculate why the overall outcome was not different in the 2 groups
c) Should any weaknesses be mentioned--

I know you are restrained by word count, but I believe expanding the discussion might help

Hope this helps
All the best
Seetha

------ End of Forwarded Message

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

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University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

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Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Word count:

Abstract: 246

Manuscript: 2671

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP is an effective evidence based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis**Error! Bookmark not defined.**[4], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks.

The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their

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exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after

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discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant, was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 05% CI 0.83, 1.01, $p=0.072$) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm,(RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP intitiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10~~15~~] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

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We prospectively identified safety outcomes that we chose to follow as investigators. These included; the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF
Date: Monday, November 16, 2009 1:40:14 PM

Great talk to you this afternoon.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 1:38 PM
To: Walsh, Michele
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Thanks for the heads up!

DSMC wants the death information shared with the other DSMCs. This is in progress.

Rose

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, November 16, 2009 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

No but I can.
Also: we have an issue: junior colleague of Neil
Was speaking about SUPPORT results at another meeting
Quite openly. We spoke to Neil, and he said he would
Take care of it. Don't know if we need to do more?
Also: was there any issue from DSMC? I was waiting to hear
Before sharing with our faculty.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 11:31 AM
To: Walsh, Michele
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

Did you send back to Neil?

-----Original Message-----

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From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, November 16, 2009 11:30 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF

A couple of suggestions highlighted In turquoise.
Biggest: I do not believe that NEJM will allow statements
Like non significant reduction in BPD: it is
Not different. Steering committee was very clear about this
Yet the language remains.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 14, 2009 2:39 AM
To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu';
'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu';
'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu';
(b) (6) 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org';
'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu';
'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu';
'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu';
'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org';
'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu';
'moshea@wfubmc.edu'; 'mcaplan@northshore.org';
'Nirupama_Laroia@URMC.Rochester.edu'; 'dale_phelps@urmc.rochester.edu';
'sduara@miami.edu'; 'nfiner@ucsd.edu'; 'wrich@ucsd.edu';
'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org';
'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu';
'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu';
'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org';
'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-
Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD)
[E]; Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 17:06:37 2009
Subject: CPAP vs SURF

Wally and Rose

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Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were opposite so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
Neil

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From: Walsh, Michele
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Date: Monday, November 16, 2009 1:39:03 PM
Attachments: SUPPORT NEJM Nov12 Final VB plus MW comments.doc

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Hi Neil: I just added a couple of edits to what Vaneeti
Suggested. My main concern is that I think you should say
BPD was not different as opposed to reduced but not statistically significant.
Talk to you soon.

Michele Walsh
Medical Director NICU
Rainbow Babies & Childrens Hospital
Case Medical Center
Professor, Deparment of Pediatrics
Case Western Reserve University
phone: 216-844-3759
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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Vivek Narendran, MD MRCP[8]; Edward Donovan[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; ~~Richard A. Ehrenkranz, MD~~ Vineet Bhandari, MD, DM[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 ~~min~~ minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP -is an effective evidence-based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 -to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] In the COIN trial surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta-analysis**Error! Bookmark not defined.**, ~~and~~ ~~a~~ A reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks was also noted in that study.

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their

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exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, ~~that~~ the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

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NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

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Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, ~~AAnn~~ $FiO_2 \leq .35$ with a SpO_2 ≥88%, a ~~mean airway pressure~~ (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on ~~high frequency ventilation~~ (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after

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discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was no significant reduction in the occurrence of BPD in the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (-RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

Comment [mw1]: Is this backwards? Control grp (surfactant is 44.3% which was lower in the CPAP 40.2%.
I do not think that you can say it was reduced: I think you can say it was the same.
Have we also looked at 40 wks? Ballard's group has found that 40 wks may be more predictive.

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for cardiac compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

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The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

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Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Subject: RE: CPAP vs SURF
Date: Monday, November 16, 2009 1:11:27 PM
Attachments: support 11-16-09dukecomments.docx

HI,,,great work Neil, Wally, and RTI for wrapping up this landmark work

here are Ron and my comments on the CPAP vs SURF latest manuscript.

our main concern is to be careful w/ the statement "The use of CPAP is an effective evidence based alternative to intubation and surfactant in preterm infants" we think that alluding to the protocol's use of cpap of +5 in the protocol, and the 'protocol-driven limited ventilator strategy' by saying "CPAP, used as described in the study protocol...' or something similar, will limit extrapolation of the study results by clinicians seeking to justify any cpap strategy for all tiny babies...and w/ COINs high mortality among the lower gestational age cohort started on cpap of +8 (13% vs 7.6% controls), we think that being specific about use of cpap as in the protocol in the conclusions is important.

there are other comments/suggestions as well, but the cautious approach to the conclusion is our biggest question.

mc

(See attached file: support 11-16-09dukecomments.docx)

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Seetha" <sshankar@med.wayne.edu>
Subject
RE: CPAP vs SURF

Hi Neil
Great to see you last week. Rose had asked me to be an "internal reviewer" for this paper. I will not be able to be on the conf call today (on my way to MLS PI meeting).
I congratulate you getting the paper written so well and so quickly. I have a few comments and am basing them on my experience with NEJM and Hypothermia RCT paper. Remember, when they are done with you, you won't recognize your paper---just kidding!

Abstract:
a) I suggest expand SUPPORT in Methods Section and BPD in Results section.
b) could you add how many of the infants in CPAP group subsequently required surfactant? I believe data is in Table 1. Also, was outcome know for all infants?
c) If you are tight for space in abstract, I suggest leave out "familial clustering" in Results and "evidence based" in the Conclusion

Introduction:
a) Expand COIN and maybe substitute "clinical center" for "unit"? also, please clarify the primary outcome of COIN trial for ease for the NEJM reader
b) I would move the SUPPORT study hypothesis to the end of the

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Introduction, before Methods

Methods
a) I suggest you take out the "purpose altered oximeters" and just say there was the oximeters arm--as you have done later. Why open a Pandora's box?
b) Substitute "NRN center" rather than "randomizing center"
c) Under sample size---can you please provide the anticipated event rate in the early CPAP arm?
d) can you clarify what the primary outcome is here (in abstract it says death or BPD, while here it appears to be death or disability--to me death or disability was a secondary outcome).
e) How was attrition rate of 17% arrived at---I think it is average loss to follow up in our FU studies---maybe you can state that?
d) Is PHY BPD a secondary outcome? I wonder if you can make the description of PHY BPD definition a little clearer---maybe "step-wise oxygen-reduction to room air challenge among infants requiring > 30% oxygen without an assistance in ventilation" or some such wording.
e) expand PMA and clarify data center at RTI International, Research Triangle Park, NC and DSMC in caps

Results
a) for the CPAP paper do you really need to say Enrollment was halted for oxygen arm etc etc? I suggest leaving it out
b) Table 1: were any other maternal variables evaluated---mode of delivery, hypertension/PET? This is a study that might be influenced by perinatal variables other than ANCS. I suggest GA be shown in completed weeks and P values to 2 decimal points only in all Tables.
c) Table 2: I am not sure I follow why unadjusted P values are given for demographic (Table 1) but adjusted for Table 2.
d) Delivery room variables, Table 4 is cited in the Results section before Table 3---maybe you can change the Table order?
e) Table 3: Why was SEM used here rather than SD? Also, suggest expand Medical and surgical NEC. PDA, IVH--preferably ICH, in footnote
f) Since the study involved 24 to 28 wk infants, why show only lower strata in Table 4????
g) Is Table 5 necessary? Again, why is P value here unadjusted?
h) Was center not a variable for adjustment or did I miss something?

Discussion
a) I am not sure I understand "higher threshold approach for intubation" Can this be clarified?
b) can you speculate why the overall outcome was not different in the 2 groups
c) Should any weaknesses be mentioned--

I know you are restrained by word count, but I believe expanding the discussion might help

Hope this helps
All the best
Seetha

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To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; Shankaran,

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'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-
Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E];
Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 17:06:37 2009
Subject: CPAP vs SURF

Wally and Rose
Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were opposite
so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
Neil

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Word count:

Abstract: 246

Manuscript: 2671

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks gestation. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol-driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 ~~min~~ minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP as described in this protocol is an effective evidence based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants, and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age, but ~~and~~ had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis.**Error! Bookmark not defined.**~~4,~~ There was also a trend toward increased mortality among the youngest strata of infants (25 – 26 weeks) randomized to CPAP (13% vs. 7.6%), but for the whole study cohort, death or the need for oxygen at 28 days was reduced in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in the composite outcome death or BPD at 36 weeks.~~and a reduction in death or the need for~~

Comment [c1]: I think it is important to point out the distinct difference in cpap 8 vs. cpap 5, and if we are reporting the good effect in the youngest subgroup, it's fair to report the poor outcome in the youngest subgroup in COIN (that was exposed to cpap+8)....this also leads me to think that particulars about how cpap was used (+5 vs. +8, may lead to very different outcomes for the most fragile kids.

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~~oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks.~~

The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol-driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purposely-altered oximeters.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation, ~~that the~~ use of early CPAP and a protocol-driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean

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airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN

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baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [12,13]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks post menstrual age (PMA) without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending

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functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. In the delivery room, ~~Surfactant~~surfactant~~,~~ was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 05% CI 0.83, 1.01, p=0.072) when adjusted for gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm,(RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

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Strata Results: 24 – 25 weeks Gestation

CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP intitiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15]

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Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

Our trial differs from the recently reported COIN trial[10~~15~~] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing and enough respiratory distress to warrant intervention~~,~~. We also included infants of 24 weeks gestation and compared the CPAP and a protocol-driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

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Comment [c2]: Making this comment about the 'complete approach' I think impacts what you can say in the conclusion about cpap in a general way....I think saying the complete approach, including cpap of 5 in the DR and limited vent strategy is what's associated w/ benefit..not just 'cpap'

We prospectively identified safety outcomes that we chose to follow as investigators. These included; the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately

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powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase

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in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. In such infants, ~~The~~ use of CPAP and a limited ventilation as described in this protocol ~~in such infants~~ is an effective evidence-based alternative to intubation and surfactant.

Comment [c3]: I think the paper will greatly influence practice....I think given the big difference between this and the COIN trial..and the mortality in the COIN trial in the youngest kids, that it's important to strongly say that the invertention that's an alternative is using the whole protocol definition, not just simply CPAP.

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From: Das, Abhik
To: Brenda B Poindexter
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: statistical review of SUPPORT school age breathing outcomes
Date: Monday, November 16, 2009 11:42:49 AM

Brenda:

Here is what I alluded to on the call today.

1. Problems with sample size calculations:
    a. Attrition may not be uniform across the 4 treatment combination cells
    b. There will be at least two pair-wise comparisons; so significance level of 5% seems too liberal
    c. It is not clear whether only marginal analyses or comparison of all 4 groups to each other is contemplated. The latter has implications for both effect size and significance level
2. Analysis plan needs to consider covariate adjustments. Even though the data is from a randomized trial, deaths and attrition likely make the benefits of randomization (with respect to covariate imbalance) moot. So, careful attention needs to be paid a priori (to discourage 'fishing') to what covariates need adjustments (or clear criteria by which these will be selected).

Hope this helps.

Thanks

Abhik

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++CONFIDENTIAL: CPAP vs SURF
Date: Monday, November 16, 2009 11:29:58 AM
Attachments: SUPPORT NEJM Nov12 Final VB plus MW comments.doc

---

A couple of suggestions highlighted In turquoise.
Biggest: I do not believe that NEJM will allow statements
Like non significant reduction in BPD: it is
Not different. Steering committee was very clear about this
Yet the language remains.

Michele Walsh
beeper (b) [redacted]
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 14, 2009 2:39 AM
To: 'mcw3@po.cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu';
'sshankar@med.wayne.edu'; 'bsood@med.wayne.edu';
'susie.buchter@oz.ped.emory.edu'; 'Anthony.Piazza@oz.ped.emory.edu';
(b) (6) [redacted]'; 'bpoindex@iupui.edu'; 'kurt.schibler@cchmc.org';
'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu';
'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu';
'alaptook@WIHRI.org'; 'vanmeurs@leland.stanford.edu';
'dwallace@rti.org'; 'wcarlo@peds.uab.edu'; 'adas@rti.org';
'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu';
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'mgantz@rti.org'; 'ifrantz@tuftsmedicalcenter.org';
'edward-bell@uiowa.edu'; 'kwatterberg@salud.unm.edu';
'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu';
'cotte010@mc.duke.edu'; 'goldb008@mc.duke.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org';
'mcunningham@rti.org'; 'petrie@rti.org'
Subject: ++++CONFIDENTIAL: CPAP vs SURF

Hi-
Here is the most recent draft of the CPAP/surfactant paper.

We will discuss on Monday's call.

Thanks for all the assistance

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD)
[E]; Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 17:06:37 2009

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Subject: CPAP vs SURF

Wally and Rose
Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were
opposite so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
Neil

Visit us at www.UHhospitals.org.

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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

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Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 ~~min~~ minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP ~~-~~is an effective evidence~~-~~based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 -to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H_20. CPAP infants were intubated if they met failure criteria.[10] In the COIN Trial surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta-analysis**Error! Bookmark not defined.**, ~~and~~ ~~a~~ A reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks was also noted in that study.

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The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their

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exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that, relative to infants managed with prophylactic/early surfactant and conventional ventilation, ~~that~~ the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

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NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

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Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, ~~AAnn~~ FiO_2 ≤ .35 with a SpO_2 ≥88%, a ~~mean airway pressure~~ (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on ~~high frequency ventilation~~ (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after

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discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [12,13]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 95% CI 0.83, 1.01, p=0.072) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, [redacted] of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm, (-RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

Comment [mw1]: Is this backwards? Control grp (surfactant is 44.3% which was lower in the CPAP 40.2%.
I do not think that you can say it was reduced: I think you can say it was the same.
Have we also looked at 40 wks? Ballard's group has found that 40 wks may be more predictive.

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP initiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

We prospectively identified safety outcomes that we chose to follow as investigators. These included: the need for cardiac compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H_2O compared to the use of early surfactant.

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The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO_2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

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Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From:	Shankaran, Seetha
To:	Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu; Gantz, Marie; Nancy Newman; Susie Buchter; Brenda Morris; Laroia, Nirupama; Sood, Beena; sduara@miami.edu; Michael O`Shea; Anthony Piazza; vineet.bhandari@yale.edu; Vivek.Narendran@cchmc.org; Phelps, Dale; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie; Shankaran, Seetha
Subject:	RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date:	Monday, November 16, 2009 11:25:06 AM

Hi Wally
Rose asked me to be internal reviewer and I won't be on call today, so here are my comments/suggestions. I congratulate you on the speed with which both you and Neil have done your respective manuscripts---you both now will hold the record for time from Data lock to Publication!

Abstract:
Results: since you do have RR and 95%CI in your Results section, maybe you don't need the P value

Methods:

a) The median actual saturation value---is this throughout the intervention period?
b) Explain how the 17% attrition was arrived at (see my comments to Neil)

Methods and/or Results

a) I wonder if you should give the citation for PHY BPD paper?
b) Table 1: Why are the N's in the this paper different from the N's in Neil's paper---are they not the same infants?
c) As mentioned re Neil's paper I wonder if other maternal characteristics should be included---PNC, Hypertension/PET, IUGR status that impact on frequency of RDS
d) Table 2: Missing data under each should be included in footnotes---then you could take off numerator /denominator and Tables will be less crowded
e) Table 2: Since this includes both primary and secondary outcomes, maybe bold the primary outcome?
f) Define Late onset sepsis---PVL is "cystic PVL"
g) Was center adjusted for---centers with more Black infants will have lower ROP
h) Figure !: This is excellent. I am intrigued by 698 who were eligible, consent not sought---even though personnel and equipment were available and the 66 for whom consent was obtained but not randomized---maybe add as footnote??? Footnotes are not counted anyway

Discussion:

a) excellent, suggest commenting on center differences if you find any.
b) How does our reduction of risk of ROP compare to Askie's?
c) Any perceived weaknesses of our trial—may as well say it (pre-emptive strike!)

Thanks for the opportunity to review. Beena is site PI from Wayne State for this and Neil's study

All the best
Seetha
I

Seetha Shankaran, MD
Professor of Pediatrics

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Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Saturday, November 07, 2009 7:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu; Gantz, Marie; Nancy Newman; Susie Buchter; Brenda Morris; Laroia, Nirupama; Sood, Beena; sduara@miami.edu; Michael O`Shea; Anthony Piazza; vineet.bhandari@yale.edu; Vivek.Narendran@cchmc.org; Phelps, Dale; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

The O2 sat paper went out without figures due to some computer glitch. Here is a copy with the 2 figures.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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619 South 20th Street
525 New Hillman Building
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Phone: 205 934 4680
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 3:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,

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Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675(b) (6) with passcode(b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases
Date: Monday, November 16, 2009 10:23:28 AM

HI,
Can I send Dale either the complete ROP adjudication cases or a sample of them?
Thanks,
Kris

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 16, 2009 10:20 AM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

thanks,

Could I see the instructions and a couple of example cases? Just to help how a clinician would interpret them?
Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 16, 2009 7:04 AM
To: Phelps, Dale
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Hi Dale,

I think that is a Rose decision and we should ask her about you adjudicating the cases. I did receive notice from Dr. Hutcheson that she fed-ex'd her cases Friday but have not heard from Dr. Markowitz yet.
Thanks,
Kris

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 16, 2009 9:59 AM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Hi Kris,
I was hoping you would let me be a score person also. I'd be happy to do the packet if you would forward.

Did Dr. Markowitz score?

Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 16, 2009 6:47 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie

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Subject: FW: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Hi Rose and Dale,

Please see below; I'm not sure how you feel about these combined results, whether that is appropriate to not.
Thanks,
Kris

From: David K Wallace [mailto:david.wallace@duke.edu]
Sent: Saturday, November 14, 2009 12:17 PM
To: Zaterka-Baxter, Kristin
Subject: Re: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Sharon Freedman I looked over several together, and we agreed on all, so we have combined our responses (attached).

DW

"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

11/09/2009 05:23 PM

To <gmarkowi@rochester.rr.com>, <david.wallace@duke.edu>, <AHUTCH2@emory.edu>, <freed003@mc.duke.edu>
cc "Das, Abhik" <adas@rti.org>
Subject NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Dear Drs. Wallace, Freedman, Hutcheson and Markowitz,

On behalf of Dr. Rose Higgins, Program Officer for the NICHD Neonatal Research Network, please find attached SUPPORT Trial cases requiring adjudication for ROP outcomes along with supporting documents to assist you with these cases to include:

- A section of the SUPPORT Trial study manual regarding the documentation of ophthalmological examinations for ROP and follow up eye outcomes
- Associated case report forms (data forms) used to collect ROP data (SUPP10 Form) and follow up eye outcomes (NF05 Form)

We would very much appreciate your response to these data by marking the appropriate check box per infant case and sending this data back to me by email or fax (contacts below) within the next 2 to 3 weeks.

Thank you in advance and please don't hesitate to contact me should you have any questions at all.
Kris

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Kris Zaterka-Baxter
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(tel) 919-485-7750
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[attachment "ROP adjudication data 30OCT09.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "MOP instructions for ROP data.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "SUPP10ROP20071015.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "NF05 Child Examination_1_16_2008.pdf" deleted by David K Wallace/EyeCenter/mc/Duke]

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases
Date: Monday, November 16, 2009 10:20:19 AM

---

great!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 7:04 AM
To: Phelps, Dale; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

We have Drs. Hutcheson and Markowitz

Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 16, 2009 10:02 AM
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

From a learning curve, figuring out what the forms showed and how to thinking about it, working together was probably very efficient and helpful (if they got it right).

On the other hand, it does not give us two independent scores which is a shame.

Did we have a 3rd adjudicator? If the 3rd agrees with the consensus, that would be fine.

If not, I would prefer to get another judgment.

Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 16, 2009 6:47 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: FW: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

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Sent: Saturday, November 14, 2009 12:17 PM
To: Zaterka-Baxter, Kristin
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Sharon Freedman I looked over several together, and we agreed on all, so we have combined our responses (attached).

DW

"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

11/09/2009 05:23 PM

To <gmarkowi@rochester.rr.com>, <david.wallace@duke.edu>, <AHUTCH2@emory.edu>, <freed003@mc.duke.edu>
cc "Das, Abhik" <adas@rti.org>
Subject NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

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Thank you in advance and please don't hesitate to contact me should you have any questions at all.
Kris

Kris Zaterka-Baxter
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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale; Zaterka-Baxter, Kristin
Cc: Gantz, Marie
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases
Date: Monday, November 16, 2009 10:06:29 AM

Should we tell these people not to collaborate, so that we have independent scores from them?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 16, 2009 10:04 AM
To: 'Phelps, Dale'; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

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Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 16, 2009 10:02 AM
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Cc: Das, Abhik; Gantz, Marie
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Sent: Monday, November 16, 2009 6:47 AM
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"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

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To <gmarkowi@rochester.rr.com>, <david.wallace@duke.edu>, <AHUTCH2@emory.edu>, <freed003@mc.duke.edu>
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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Cc: Das, Abhik; Gantz, Marie
Subject: FW: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases
Date: Monday, November 16, 2009 9:46:52 AM
Attachments: ROP ADJUDICATION Freedman Wallace.docx

Hi Rose and Dale,

Please see below; I'm not sure how you feel about these combined results, whether that is appropriate to not.
Thanks,
Kris

From: David K Wallace [mailto:david.wallace@duke.edu]
Sent: Saturday, November 14, 2009 12:17 PM
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Subject: Re: NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

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"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

11/09/2009 05:23 PM

To <gmarkowi@rochester.rr.com>, <david.wallace@duke.edu>, <AHUTCH2@emory.edu>, <freed003@mc.duke.edu>
cc "Das, Abhik" <adas@rti.org>
Subject NICHD Neonatal Research Network SUPPORT Trial ROP Adjudication Cases

Dear Drs. Wallace, Freedman, Hutcheson and Markowitz,

On behalf of Dr. Rose Higgins, Program Officer for the NICHD Neonatal Research Network, please find attached SUPPORT Trial cases requiring adjudication for ROP outcomes along with supporting documents to assist you with these cases to include:

- A section of the SUPPORT Trial study manual regarding the documentation of ophthalmological examinations for ROP and follow up eye outcomes
- Associated case report forms (data forms) used to collect ROP data (SUPP10 Form) and follow up eye outcomes (NF05 Form)

We would very much appreciate your response to these data by marking the appropriate check box per infant case and sending this data back to me by email or fax (contacts below) within the next 2 to 3

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weeks.

Thank you in advance and please don't hesitate to contact me should you have any questions at all.
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

[attachment "ROP adjudication data 30OCT09.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "MOP instructions for ROP data.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "SUPP10ROP20071015.pdf" deleted by David K Wallace/EyeCenter/mc/Duke] [attachment "NF05 Child Examination_1_16_2008.pdf" deleted by David K Wallace/EyeCenter/mc/Duke]

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ROP ADJUDICATION

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From: Cunningham, Meg
To: mcaplan@northshore.org; Walsh, Michele; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; [SCRN] Stoll, Barbara; kurt.schibler@cchmc.org; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; Laptook, Abbot; vanmeurs@leland.stanford.edu; wcarlo@peds.uab.edu; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; Ifrantz@tufts-nemc.org; Roger.Faix@hsc.utah.edu; Kristi Watterberg; edward-bell@uiowa.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu
Cc: StWilliams@peds.uab.edu; gonza025@mc.duke.edu; bvecchio@careNE.org; lmoore@med.wayne.edu; jwaidne@emory.edu; Rose, Joyce; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Irene, Amanda; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; Nancy.M.Smith@uth.tmc.edu
Subject: RE: SC Call to discuss SUPPORT papers
Date: Monday, November 16, 2009 8:34:50 AM

Reminder for today's call.

From: Webb, Robin E.
Sent: Tuesday, November 03, 2009 4:46 PM
To: Webb, Robin E.; 'mca113@northwestern.edu'; 'Walsh, Michele'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'sshankar@med.wayne.edu'; [SCRN] Stoll, Barbara; 'kurt.schibler@cchmc.org'; 'bpoindex@iupui.edu'; 'richard.ehrenkranz@yale.edu'; 'Laptook, Abbot'; 'vanmeurs@leland.stanford.edu'; 'wcarlo@peds.uab.edu'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'Ifrantz@tufts-nemc.org'; 'Roger.Faix@hsc.utah.edu'; 'Kristi Watterberg'; 'edward-bell@uiowa.edu'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; 'Bradley.Yoder@hsc.utah.edu'; Gantz, Marie; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'
Cc: 'StWilliams@peds.uab.edu'; 'gonza025@mc.duke.edu'; 'bvecchio@careNE.org'; 'lmoore@med.wayne.edu'; 'jwaidne@emory.edu'; 'Rose, Joyce'; 'archerst@mail.nih.gov'; Cunningham, Meg; Zaterka-Baxter, Kristin; Irene, Amanda; 'fmartinez@ucsd.edu'; 'Carolyn.Grier@UHhospitals.org'; Cunningham, Meg; 'Nancy.M.Smith@uth.tmc.edu'
Subject: SC Call

The call to discuss the final versions of the two papers for the SUPPORT study has been scheduled as detailed below. We picked the time that worked for the most number of people. if you are unable to make this time, please have your co-PI or coordinator join.

Monday, 11/16
4:00pm ET

Dial:
Within the USA
866-675-(b) (6)
or

Outside the USA
1-203-310-(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From: Wally Carlo, M.D.
To: Finer, Neil; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE:
Date: Saturday, November 14, 2009 1:29:20 PM

Hi Neil.
I did something like that. I do not have it with me now and don't recall the exact one.

Wally

-----Original Message-----
From: Finer, Neil <nfiner@ucsd.edu>
Sent: Saturday, November 14, 2009 1:59 PM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Rich, Wade <wrich@ucsd.edu>
Subject:

Hi Wally
This title that I used for the CPAP Surf is within NEJM requirements
Can you use this template ie "Low versus high oximetry ranges in very preterm infants: The SUPPORT Trial"
Look forward to talking to you on Monday
Be well
Neil

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CPAP vs SURF
Date: Saturday, November 14, 2009 11:46:12 AM

Rose
You know the journal better than I - go ahead and have a talk with them
I'll talk to you on Monday
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 13, 2009 11:42 PM
To: 'wcarlo@peds.uab.edu'; Finer, Neil; Rich, Wade
Subject: Re: CPAP vs SURF

If you want both papers to appear in the same issue of any jornal, we would need to proactively state this. Otherwise, the publications may appear at different times. If everyone is ok with this, that is fine. It would be ideal (perhaps too optimistic) to have them appear simultaneously in the literature.

Rose

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Fri Nov 13 14:36:43 2009
Subject: RE: CPAP vs SURF

I do not feel strongly either way

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 13, 2009 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
Subject: Re: CPAP vs SURF

Why would we give them an ultimatum?
I think both papers stand well enough alone and NEJM is NOT the only option
What to the rest of you think. I am sure Peds would take then both.
Neil

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On 11/13/09 10:09 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> DO you want this sent to the steering committee in advance of the call on
> Monday??
>
> Also, David Stevenson's title suggestion can easily be incorporated in both
> papers. Yours could be :
> The SUPPORT Trial: Early CPAP....
>
> Wally's could be
> The SUPPORT Trial: Oximetry.....
>
> If we use the two titles, I will contact NEJM and tell them it's both or none
> if everyone (including the SC agrees)
>
> let me know
>
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the NICHD Neonatal Research Network
> _____
> From: Finer, Neil [nfiner@ucsd.edu]
> Sent: Thursday, November 12, 2009 5:06 PM
> To: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
> Subject: CPAP vs SURF
>
> Wally and Rose
> Here is the 'final' CPAP vs Surf paper
> It fits NEJM and incorporates all suggestions although some were opposite so
> we made some choices.
> Please review
> Wally can you make sure our definitions for BPD etc are identical??
> Thanks
> I would like to get these submitted
> Please share with me your thoughts
> Be well
> Neil

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CPAP vs SURF
Date: Saturday, November 14, 2009 5:03:17 AM

I agree it would be best to have them together.

Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Saturday, November 14, 2009 1:42 AM
To: 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'wrich@ucsd.edu' <wrich@ucsd.edu>
Subject: Re: CPAP vs SURF

If you want both papers to appear in the same issue of any jornal, we would need to proactively state this. Otherwise, the publications may appear at different times. If everyone is ok with this, that is fine. It would be ideal (perhaps too optimistic) to have them appear simultaneously in the literature.

Rose

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From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Sent: Fri Nov 13 14:36:43 2009
Subject: RE: CPAP vs SURF

I do not feel strongly either way

Wally Carlo, M.D.
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Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 13, 2009 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade
Subject: Re: CPAP vs SURF

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What to the rest of you think. I am sure Peds would take then both.
Neil

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<higginsr@mail.nih.gov> wrote:

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> The SUPPORT Trial: Early CPAP....
>
> Wally's could be
> The SUPPORT Trial: Oximetry.....
>
> If we use the two titles, I will contact NEJM and tell them it's both or none
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> Here is the ³final² CPAP vs Surf paper
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> Please review
> Wally can you make sure our definitions for BPD etc are identical??
> Thanks
> I would like to get these submitted
> Please share with me your thoughts
> Be well
> Neil

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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo; Rich, Wade
Subject: RE: CPAP vs SURF
Date: Friday, November 13, 2009 10:48:12 PM

I will have mine on monday. I have done a revision in response to all the comments I got but the secretaries did not finished typing it.

Wally

-----Original Message-----
From: Finer, Neil <nfiner@ucsd.edu>
Sent: Friday, November 13, 2009 9:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Cc: Wally Carlo <wcarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Subject: Re: CPAP vs SURF

Sure

Sent from my iPhone

On Nov 13, 2009, at 10:12 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov > wrote:

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> Also, David Stevenson's title suggestion can easily be incorporated
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> Rosemary D. Higgins, MD
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> I would like to get these submitted
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> Be well
> Neil

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: O2 sat manuscript
Date: Friday, November 13, 2009 7:52:40 PM

Hi Rose:

Marsha could not finish the manuscript today but Cassandra will do it on Monday AM.

One question: I was not going to put a table in the text but include it in the appendix as NEJM has table/figure limitation. I will have a statement in the paper saying cause of death did not differ. We can also put all data in the text. What do you think?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
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Cell: 205 266 (b) (6)

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From: Finer, Neil
To: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: CPAP vs SURF
Date: Thursday, November 12, 2009 5:04:49 PM
Attachments: SUPPORT NEJM Nov12 Final.doc
NEJM Tables Nov 10.doc

Wally and Rose
Here is the "final" CPAP vs Surf paper
It fits NEJM and incorporates all suggestions although some were opposite so we made some choices.
Please review
Wally can you make sure our definitions for BPD etc are identical??
Thanks
I would like to get these submitted
Please share with me your thoughts
Be well
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Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Vivek Narendran, MD MRCP[8]; Edward Donovan[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University

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of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22] University of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

Neil N Finer, M.D. Phone: (919) 543 3285

University of California at San Diego Fax: (619) 543 3812

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San Diego, CA 92103-8774 Email: nfiner@ucsd.edu

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilation strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced in the CPAP group compared to the surfactant group, (48.7% vs 54.1%, RR 0.91, 95% CI 0.83, 1.01, p=0.072 when adjusted for gestational age, center and familial clustering. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011) and fewer required intubation or post natal steroids for BPD, (p<.001). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03).

Conclusions: The use of CPAP is an effective evidence based alternative to intubation and surfactant in preterm infants.

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Introduction:

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[12] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[3] There is now a growing body of evidence suggesting a benefit for early CPAP for preterm infants with RDS .[456] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following early CPAP.[789]

The recent COIN trial randomized 610 infants from 25 0/7 to 28 6/7 weeks gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[10] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis**Error! Bookmark not defined.**[4], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with a non significant decrease in death or BPD at 36 weeks.

The SUPPORT Trial was designed to compare early CPAP to early surfactant for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their

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exposure to oxygen using a factorial design. The results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324). This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at a randomizing center, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to two gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU. CPAP infants were not to be intubated exclusively for surfactant administration in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications.[11]

NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard practice.

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Surfactant Arm: All infants were to be intubated in the delivery room and receive surfactant within 1 hour of life, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable without evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, with multiples randomized to the same arm.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months by 10%, based on year 2000 NRN baseline occurrence data. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after

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discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not powered for an interaction effect between the 2 factorial arms.

There was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which assigned the diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks. [1213]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each group who survived to 36 weeks PMA without BPD. Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age strata, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock or O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included

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death, pneumothorax, intraventricular hemorrhage and the need for chest compressions or epinephrine in the delivery room.

The study was approved by Human Subjects Committees at all sites and RTI, the NRN data center. Parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled from Feb 2005 through Feb 2009. Enrollment was temporarily suspended from November 2005 until February 2006 by the DSMB because of concerns regarding the oximetry data; no protocol changes were made. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, or race between the 2 treatment groups (Table 1).

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant. Surfactant, was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7% versus 54.1%, (RR 0.91, 05% CI 0.83, 1.01, $p=0.072$) when adjusted for

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gestational age, center and familial clustering as pre-specified. Death during the hospitalization was 3.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 23.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, there was a non-significant reduction in the occurrence of BPD based on the use of supplemental oxygen, from 40.2% for the CPAP arm to 44.3% for the Surfactant arm,(RR 0.94, 95% CI 0.82, 1.06). Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs. 40.6%, RR 0.99, 95% CI 0.87, 1.14). Death or Physiologic BPD at 36 weeks in the CPAP group was 47.8% vs. 51.0% for the Surfactant group, (RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, length of stay, days of oxygen for survivors, or discharge on oxygen (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All but 2 infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants (7.2 % vs 13.2%, p<0.001).

Strata Results: 24 – 25 weeks Gestation

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CPAP infants had a significantly lower mortality while hospitalized 23.9% vs. 32.1%. Causes of death are reported in Table 5. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs. 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[14] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3% vs. 31.4%, RR=0.75, 95% CI 0.54, 1.05).

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.8% vs 10.2%. The CPAP infants required fewer days of oxygen, 44.0 vs 49.5, p=0.035. Significantly fewer infants received postnatal steroids for BPD, 2.9% vs 7.9%, p=0.008.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare CPAP intitiated in the delivery room with early surfactant in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention that enrolled infants of 24 weeks gestation. Earlier we found that 100% of infants of 23 weeks gestation required intubation in the DR, and decided that such infants would unlikely be successfully treated with CPAP alone.[15] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[16]

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Our trial differs from the recently reported COIN trial[10~~15~~] in that we randomized all eligible ELBW infants irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who were to receive surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of comparing current NRN practice in a number of centers with previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation.[6,7] We believed that testing this complete approach would provide a more relevant result as units currently using early CPAP tend to have a higher threshold for intubation.

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We prospectively identified safety outcomes that we chose to follow as investigators. These included; the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we prospectively agreed to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

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Our study has demonstrated that intent-to-treat with early CPAP and a strategy of limited ventilation compared to surfactant given within 1 hour of birth was associated with a non-significant decrease in death by 36 weeks PMA or BPD as defined by the need for oxygen at 36 weeks from 54.1% to 48.7%. We also noted a significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.2 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that the lower incidence of death in this strata along with significantly decreased durations of mechanical ventilation, a decreased need for intubation and exposure to post natal steroids and a reduction in BPD in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Conclusions:

Compared with infants randomized to be intubated in the delivery room and receive surfactant within 1 hour of birth, infants between 24 and 27 6/7ths weeks gestation assigned to treatment with CPAP and a strategy of limited ventilation have a non significant reduction in the incidence of death or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcome. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)	0.9686
	26-27	57.0% (378/663)	57.1% (373/653)	
Male		51.6% (342/663	56.7% (370/653	0.0646
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)	0.3681
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)	
	Hispanic	20.8% (138/663)	18.5% (121/653)	
	Other/unknown	3.2% (21/663)	4.0% (26/653)	
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Antenatal steroids (any)		96.8% (642/663	95.6% (623/652	0.2248
Antenatal steroids (full course)		73.6% (486/660	69.8% (453/649	0.1232
Death in the DR (per SUPP03/SUPP04)		0.2% (1/663)	0.8% (5/653)	0.0978

Table 2. Delivery Room Status and Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661	25.6% (167/653	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662	92.9% (606/652	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663	22.4% (146/653	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660	93.4% (609/652	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660	27.0% (176/652	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67.1% (443/660	98.9% (646/653	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Death at any time while hospitalized	16.4% (109/663	19.6% (128/653	0.84 (0.67, 1.05)	0.1259
Total LOS any hospital* Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
Days on supplemental oxygen† Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
Discharge on oxygen	22.2% (122/550	23.9% (124/519	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655	48.8% (318/652	1.14 (1.03, 1.25)	0.0111
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC	12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery	11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4	14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
Postnatal steroids for BPD	7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. Outcomes for 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week	8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Total LOS any hospital* Mean±StdErr (N=407)	122.0 ± 2.9	119.0 ± 3.1		0.4690
Days on supplemental oxygen† Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) † Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
Discharge on oxygen	32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery	16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 5. Cause of Death - 24-25 week Strata

Variable	Category	CPAP (N=68)	Surfactant (N=90)	Unadjusted P-value
Contributory cause of death	1=RDS	13/68 (19.1)	31/90 (34.4)	0.1212
	2=BPD	10/68 (14.7)	7/90 (7.8)	
	3=Infection	14/68 (20.6)	15/90 (16.7)	
	4=NEC	10/68 (14.7)	16/90 (17.8)	
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)	
	6=Immaturity	3/68 (4.4)	5/90 (5.6)	
	7=Other	7/68 (10.3)	11/90 (12.2)	

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu
Cc: wrich@ucsd.edu
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Thursday, November 12, 2009 3:19:39 PM

It may be good to emphasize two interventions rather than two outcomes as some may think we separated the outcomes into two papers.

Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Thursday, November 12, 2009 3:12 PM
To: 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>
Cc: 'wrich@ucsd.edu' <wrich@ucsd.edu>
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

I think the two titles could be;

SUPPORT Trial: ventilatory management outcomes

SUPPORT Trial: saturation target outcomes

Or something to that effect

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo <wcarlo@peds.uab.edu>
Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Thu Nov 12 14:26:41 2009
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Dear Rose
Wade and I will develop a final CPAP-Surf paper and Wally will develop the oximeter paper
_ I don't follow David's suggestion and I think we should proceed as planned
The only modification we could consider is to list the subcommittee and the indicate the PI. I am OK with what we are doing.
Our final paper will incorporate all suggestions to date where feasible nd be of appropriate length – 2700 words and abstract 250 words etc.
We will get this to you within the next 5 days. Wally can you do the same for your paper??
Rose I would like to indicate to the NRN that we have received all the input we need and we will now modify and submit.
Otherwise this process will take forever. We should let the journal have their input
The only question is whether we think that the results are important enough for an expedited process??
I would probably say no and go ahead and submit the 2 together

Neil

On 11/12/09 9:09 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the comments below for the papers. This is the second "internal review."

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Av had done the first one and I know he has corresponded with both of you.

I think David's comment about the title is important and I can contact nejm in advance of submission

Thanks
Rose

From: David Stevenson <dstevenson@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Nov 12 11:48:51 2009
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Rose,

I reviewed the companion papers and have some general comments about each as well as some minor editorial suggestions.

Finer's Paper

Although I believe there is some logic to reporting the two parts of this trial separately but as companion papers, there is the risk that one can be reported without the other, at least initially (unless there is some agreement in advance). I hope this will be unlikely as the two are inextricably intertwined in the actual trial as it was conceived. For this reason, I believe that each should bear the title of Neil's first author primary paper, which then deserves a subtitle indicating what part of the trial is being presented and discussed. With respect to the paper for which Wally is the first author, it needs the general title from Finer's paper and it should retain the subtitle as proposed by Wally.

In the abstract in the Results section, without going to the tables, the last two sentences are confusing with respect to their linkage. That is, the first statement is focused clearly on the 24-25 weeks stratum. The latter applies to the whole group, including the larger infants. Thus, the second statement should make this clear otherwise the reader will link the two statements. Likewise in the Conclusion section of the abstract, there is reference to "such" infants. The naïve reader will not know based upon the proceeding section to what "such" infants refers.

In the Introduction section of the manuscript, there is a statement that "overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI)." Presumably this is related to reference 14, but the proceeding review does not seem to justify the part of the sentence that says "may do so for the most immature infants," although such a statement is a desirable preamble to the present study. What is the evidence for this statement?

At the end of the Introduction, the last sentence seems like an "add on," although it is essential to the design of the trial. I realize that is the topic of the second paper, but more may need to be said about the actual design of the study and its incorporation of an oximetry randomization.

In the Methods section, the reference "purpose-altered" oximeters is not informative. A naïve reader would not know what is meant and the oximetry part of the trial would not be discussed in this paper as proposed.

In the section on the CPAP Arm, there is a statement "CPAP infants were not to be intubated for surfactant only in the DRŠ." Although it becomes clear later in the paper, it is not clear at this point what this means - whether the infants are not to be intubated just because someone wants to give them surfactant or that they were not to be intubated for surfactant only in the DR, but could be intubated later for this purpose. This should be clarified at this point in the paper.

In the NICU management section, "clinically significant patent ductus arteriosus" will need to be defined. In the Results section, the statement about the primary outcome and the other important findings with respect to the 24-25 stratum should be moved to the beginning of this section followed by the other statistics. This might require reordering of the tables but they are out of order at this point anyway with reference to Table 4 occurring before

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Table 3. Also in this section, I think that the reference to "non-significant" reductions is not useful. Either a finding is statistically significant or it is not based upon the criteria set in advance. The results can simply be stated if a trend needs to be pointed out to the reader. This is done several times in this section. This kind of phraseology is also used in the Discussion and should be avoided.

In the Discussion, one of the paragraphs ends with the statement that "we believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygenationŠ represents a substantial clinical benefit compared with the initial use of early surfactant." Most of this opinion seems unsubstantiated by the actual data in this study. Perhaps a more measured interpretation would be reasonable.

Although there is a statement that the study was not powered to detect interaction between the two interventions (one of which was not discussed in this paper) and the evaluation of such interactions was done and none were found. This is an unusual statement and it is at least paradoxical. Unfortunately, it is probably unavoidable.

In the Conclusions section, the statement should focus on the primary outcome which is negative and the secondary outcome which is perhaps the most important finding related to the 24-25 week stratum. The last paragraph of the paper should be rewritten to reflect the major findings.

Wally's Paper

Wally's paper needs to have the same title as Neil's paper using the currently proposed title as the subtitle.

In the second paragraph of the Introduction, in reference to the survey, the statistics are confusing because the comparisons in the parentheses are not explicit. Unless one went to reference 5, the statement would not be clear. In the Methods Section, in the paragraph on "Assessments," would the reference to the primary outcome as death before discharge and/or threshold retinopathy of prematurity be sufficiently characterized with only an "and" or "or?" Is it one or the other or really both? In one place, in the "Statistical analysis" section and in several places in the Results, there are missing numbers which I assume will be supplied.

Once again in the Discussion, I would recommend starting the section with the major finding first and then moving into the history. This discussion is reminiscent of the one for the phototherapy manuscript, where secondary tradeoffs are interacting in important ways, "teeing up" difficult decisions.

This manuscript is a little more clear than Neil's (probably because I read it second) in its current form and requires only minor edits. A major issue is the fact that interactions between these two interventions (ventilatory and oxygenation) cannot be fully elucidated. This will be frustrating to some readers, but it is unavoidable. Another unavoidable circumstance is the tremendous overlap of the targets which will frustrate or limit further interpretation of the results.

Congratulations to Neil and others for conducting a very difficult trial which is important and provocative.

Sincerely yours,
David

Thanks!!!
Rose

----- Original Message -----
From: David K. Stevenson <dstevenson@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 06 18:01:13 2009
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Rose,

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I can do it.

David

----- Original Message -----
From: "Rosemary Higgins (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Ed Donovan" <edward.donovan@cchmc.org>, "Avroy' 'Fanaroff" <Avroy.Fanaroff@UHhospitals.org>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "jon e tyson" <jon.e.tyson@uth.tmc.edu>
Cc: "Wally" <wcarlo@peds.uab.edu>, nfiner@ucsd.edu
Sent: Friday, November 6, 2009 1:45:40 PM GMT -08:00 US/Canada Pacific
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,

You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,

Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

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This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 - 4 PM - call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-3256 with passcode 560152#

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd. , Room 4B03

MSC 7510

Bethesda , MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Thursday, November 12, 2009 2:12:55 PM

Third option one for each.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 10, 2009 10:09 AM
To: Walsh, Michele
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Saturation paper

Michele – can you respond to this question:

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
_____ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
_____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

---

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, November 10, 2009 9:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

yes

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 12:27 PM
To: 'Finer, Neil'; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; Roger Faix; Brad Yoder (Bradley.yoder@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

Kurt has proposed an alternative for the CPAP/surf paper. As many of you are likely to recall, Ed Donovan organized the SUPPORT training and the video in 2004. Let me know if ED and Vivek can appear on the CPAP/surf paper.

Thanks
Rose

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From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, November 09, 2009 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper
Importance: High

Hi Rose,
Personally, I would like to advocate that Ed Donovan and Vivek Narendran both be listed as Cincinnati authors on the CPAP Surfactant manuscript since Ed and Vivek did a lot to move forward the study up front and Vivek was instrumental during the trial. (Ed did a lot with initial start up and education, hosting the training, producing the training video, and was the Cincinnati PI at the beginning of the study). I would like to be listed as the author from Cincinnati on the Oxygen Saturation.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736(b)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
___X__ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
_____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

_____ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

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Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,

Just wondering,

Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.

Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Thursday, November 12, 2009 12:38:58 PM

Rose:

I had communited with Neil about the title as NEJM has a 75 character limit and the new guidelines from many journals prefer the term random or similar term in the title, if pertinent. I assume we could have different titles with the subtitle "The SUPPORT Trial" as abbreviation or expanded.

wally

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 11/12/2009 11:09 AM
To: 'nfiner@ucsd.edu'; Wally Carlo, M.D.
Subject: Fw: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

See the comments below for the papers. This is the second "internal review."
Av had done the first one and I know he has corresponded with both of you.

I think David's comment about the title is important and I can contact nejm in advance of submission

Thanks
Rose

From: David Stevenson <dstevenson@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Nov 12 11:48:51 2009
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Rose,

I reviewed the companion papers and have some general comments about each as well as some minor editorial suggestions.

Finer's Paper

Although I believe there is some logic to reporting the two parts of this trial separately but as companion papers, there is the risk that one can be reported without the other, at least initially (unless there is some agreement in advance). I hope this will be unlikely as the two are inextricably intertwined in the actual trial as it was conceived. For this reason, I believe that each should bear the title of Neil's first author primary paper, which then deserves a subtitle indicating what part of the trial is being presented and discussed. With respect to the paper for which Wally is the first author, it needs the general title from Finer's paper and it should retain the subtitle as proposed by Wally.

In the abstract in the Results section, without going to the tables, the last two sentences are confusing with respect to their linkage. That is, the first statement is focused clearly on the 24-25 weeks stratum. The latter applies to the whole group, including the larger infants. Thus, the second statement should make this clear otherwise the reader will link the two statements. Likewise in the Conclusion section of the abstract, there is reference to "such"

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infants. The naïve reader will not know based upon the proceeding section to what "such" infants refers.

In the Introduction section of the manuscript, there is a statement that "overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI)." Presumably this is related to reference 14, but the proceeding review does not seem to justify the part of the sentence that says "may do so for the most immature infants," although such a statement is a desirable preamble to the present study. What is the evidence for this statement?

At the end of the Introduction, the last sentence seems like an "add on," although it is essential to the design of the trial. I realize that is the topic of the second paper, but more may need to be said about the actual design of the study and its incorporation of an oximetry randomization.

In the Methods section, the reference "purpose-altered" oximeters is not informative. A naïve reader would not know what is meant and the oximetry part of the trial would not be discussed in this paper as proposed.

In the section on the CPAP Arm, there is a statement "CPAP infants were not to be intubated for surfactant only in the DRŠ." Although it becomes clear later in the paper, it is not clear at this point what this means - whether the infants are not to be intubated just because someone wants to give them surfactant or that they were not to be intubated for surfactant only in the DR, but could be intubated later for this purpose. This should be clarified at this point in the paper.

In the NICU management section, "clinically significant patent ductus arteriosus" will need to be defined. In the Results section, the statement about the primary outcome and the other important findings with respect to the 24-25 stratum should be moved to the beginning of this section followed by the other statistics. This might require reordering of the tables but they are out of order at this point anyway with reference to Table 4 occurring before Table 3. Also in this section, I think that the reference to "non-significant" reductions is not useful. Either a finding is statistically significant or it is not based upon the criteria set in advance. The results can simply be stated if a trend needs to be pointed out to the reader. This is done several times in this section. This kind of phraseology is also used in the Discussion and should be avoided.

In the Discussion, one of the paragraphs ends with the statement that "we believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygenationŠ represents a substantial clinical benefit compared with the initial use of early surfactant." Most of this opinion seems unsubstantiated by the actual data in this study. Perhaps a more measured interpretation would be reasonable.

Although there is a statement that the study was not powered to detect interaction between the two interventions (one of which was not discussed in this paper) and the evaluation of such interactions was done and none were found. This is an unusual statement and it is at least paradoxical. Unfortunately, it is probably unavoidable.

In the Conclusions section, the statement should focus on the primary outcome which is

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negative and the secondary outcome which is perhaps the most important finding related to the 24-25 week stratum. The last paragraph of the paper should be rewritten to reflect the major findings.

Wally's Paper

Wally's paper needs to have the same title as Neil's paper using the currently proposed title as the subtitle.

In the second paragraph of the Introduction, in reference to the survey, the statistics are confusing because the comparisons in the parentheses are not explicit. Unless one went to reference 5, the statement would not be clear. In the Methods Section, in the paragraph on "Assessments," would the reference to the primary outcome as death before discharge and/or threshold retinopathy of prematurity be sufficiently characterized with only an "and" or "or?" Is it one or the other or really both? In one place, in the "Statistical analysis" section and in several places in the Results, there are missing numbers which I assume will be supplied.

Once again in the Discussion, I would recommend starting the section with the major finding first and then moving into the history. This discussion is reminiscent of the one for the phototherapy manuscript, where secondary tradeoffs are interacting in important ways, "teeing up" difficult decisions.

This manuscript is a little more clear than Neil's (probably because I read it second) in its current form and requires only minor edits. A major issue is the fact that interactions between these two interventions (ventilatory and oxygenation) cannot be fully elucidated. This will be frustrating to some readers, but it is unavoidable. Another unavoidable circumstance is the tremendous overlap of the targets which will frustrate or limit further interpretation of the results.

Congratulations to Neil and others for conducting a very difficult trial which is important and provocative.

Sincerely yours,
David

Thanks!!!
Rose

----- Original Message -----
From: David K. Stevenson <dstevenson@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 06 18:01:13 2009
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Rose,

I can do it.

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David

----- Original Message -----
From: "Rosemary Higgins (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Ed Donovan" <edward.donovan@cchmc.org>, "Avroy' 'Fanaroff" <Avroy.Fanaroff@UHhospitals.org>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "jon e tyson" <jon.e.tyson@uth.tmc.edu>
Cc: "Wally" <wcarlo@peds.uab.edu>, nfiner@ucsd.edu
Sent: Friday, November 6, 2009 1:45:40 PM GMT -08:00 US/Canada Pacific
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,

You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole

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Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,

Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 - 4 PM - call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675(b) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD

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Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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From: Kurt Schibler
To: Poindexter, Brenda B
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcomes
Date: Thursday, November 12, 2009 11:33:30 AM
Attachments: Breathing Outcomes Review_KS.doc

Hi Brenda,

I will not be available for the protocol subcommittee call on Breathing Outcomes, but have attached a few comments. I am enthusiastic about the study and feel it should move forward. If significant concerns arise I will discuss with you when I return.

Kind Regards!

Kurt

Kurt Schibler, MD
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Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
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Protocol Review
November 2009

SUPPORT - School Age Breathing Outcomes Study: A Proposal for the NICHD Neonatal Research Network
October 21, 2009
Investigators: Timothy P. Stevens, MD, MPH; Richard A. Ehrenkranz, MD; Neil N. Finer, MD

Comments by Kurt Schibler, MD

I am enthusiastic about this study and would like to see it move forward. Here are a few comments for the discussion next week.

1. I would advocate for comparing environmental tobacco exposure in CPAP versus intubation/surfactant arm in addition to the high versus low saturation arm. I do not see this proposed, but the first hit of oxygen may have a quite different than that of an endotracheal tube and microbial colonization.
2. Are cotinine levels being measured at 18-22 months and at 6-7 years for ETS?
3. How are other environmental exposures being evaluated?
4. The comparisons of subgroups with and without BPD should be stratified by gestational age group or correct for gestational age to assure that the groups have similar lung development at the time of the insults.
5. While there is separation in oxygen exposure between high and low O2 saturation groups, there is significant overlap. If there are sufficient patients, might the investigators want a priori to set up a look at highest versus lowest quartile oxygen exposure as well.
6. Perhaps the pulmonologists know how an 8% change in PFT's correlated with respiratory symptoms, need for pulmonary care, or impacts lifestyle (sedentary versus active choices). I think these correlations should be analyzed. In other words what is the clinical and lifestyle significance of this degree of change in PFTs?

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From: Kurt Schibler
To: Finer, Neil; Wally Carlo
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Edward Donovan
Subject: CPAP /Surf paper
Date: Thursday, November 12, 2009 9:05:08 AM
Attachments: SUPPORT Manuscript - Network Version Word Nov 6 09 KS.doc

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Hi Neil,
The manuscript looks great! I do have a couple suggested changes and comments (tracking changes/comments on attachment). My most significant comments are:
1. Vivek Narendran should be listed as the Cincinnati author for the CPAP paper. I have advocated that Ed Donovan also be an author as he did a great deal of work leading up to this trial, hosted the education session, produced the video and was the PI here for the first two years of the trial. Of course this decision is up to the steering committee.
2. The definition of BPD should be consistent between the CPAP and Oximetry manuscripts and should be clear in the Methods. I would favor the physiologic definition. Oxygen at 36 weeks should also be reported as you have for comparisons with other trials.
3. I think the term non-significant reduction is overused and should be reserved for use only if results are very close to significance.
4. In the discussion in the 24-25 week strata, BPD and ROP are reported as reduced. BPD is not significantly reduced and ROP is not reported in that strata.

Ed Donovan will be on the call Monday. I will not as I will be out of the country and with limited to no internet access.

Thanks for your passion, hard work, and inspiration!!
Kurt

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; ~~Kurt Schibler~~Vivek Narendran, MD MRCP[8]; Edward Donovan, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University

Comment [cc1]: If OK by Steering Committee

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of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]Univresity of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) -- Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Word count:

Abstract: 250

Manuscript: 3079

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, **defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering),** There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001).

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Comment [cc2]: The definition of BPD should be the consistent in both arms of the SUPPORT Trial. In the Oximentry paper it is reported as the physiological definition of BPD

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Conclusions: The use of CPAP in ~~such~~ infants 24 to 28 weeks gestation is an effective evidence based alternative to intubation and surfactant.

Comment [cc3]: Or extremely premature

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation. Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[44], and a reduction in death or the need for oxygen at 28

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days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited

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ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Comment [cc4]: Neil, I think BPD should be defined here and should be consistent between manuscripts. I favor the physiological definition.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications **(need ref)** including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While

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intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within one hour of intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standardpractice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 $\geq$88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), -and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% -using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

Comment [cc5]: This is a long sentence. It might be broken into hypothsis and then a second sentence giving the baselines.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

Comment [cc6]: This is confusing because BPD is not defined in the methods, only in the abstract. Again it should be defined with primary outcome and this can be included there. It should be consistently reported in the two manuscripts.

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was

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known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. (Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through to Mar 1 2009-. The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or

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race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all p<0.001). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, p<0.001, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, p=0.060) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP

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Comment [cc7]: Define BPD in methods

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Comment [cc8]: I think non-significant reduction is overused, a RR of 0.99 with these confidence intervals is not different.

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infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. **The differences are shown in Table 4 (24-25 wk Strata).** CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

Comment [cc9]: These racial and ethnic differences are not shown in table 4.

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26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other ~~outcome~~intervention -that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[~~15~~15] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that early CPAP and protocol driven limited ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with- reductions in **BPD, ROP**, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

Comment [cc10]: This is not shown in the table. BPD is not significantly reduced and ROP is not discussed in this strata.

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We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Tinsley, Mazie L.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Wednesday, November 11, 2009 9:26:02 AM

Good Morning,

Dr. Higgins I am printing the papers out for Dr. Stoll's review, however there was only one paper attached. The one attached was Dr. Finer's -

Is it possible for you to send me the other paper? Thank you very much

---

From: Barbara Stoll [Barbara.Stoll@oz.ped.emory.edu]
Sent: Tuesday, November 10, 2009 11:21 PM
To: Tinsley, Mazie L.
Subject: Fwd: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
Office: 404-727-2456 Fax: 404-727-5737
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----- Original Message -----

Hi Again
The previous version was unreadable by most – Sorry for that
Here is a Word doc that I hope all can read
Neil

On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

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On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Wally Carlo, M.D.
To: Roger Faix
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Bradley Yoder
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Tuesday, November 10, 2009 7:08:07 PM

Hi Roger:

Thanks for the thoughtful comments. I will work on these.
We have causes of death. There is no pattern to it.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Tuesday, November 10, 2009 6:06 PM
To: Wally Carlo, M.D.
Cc: nfiner@ucsd.edu; higginsr@mail.nih.gov; Bradley Yoder
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Wally!

I had the opportunity to read the most recent version of the manuscript that you forwarded. I remain impressed by your ability to rapidly generate a concise manuscript about a complex study. I do have a few thoughts/suggestions:

1) On page 1 of the title page, my name should have the superscript 6 next to it (Utah), rather than 5 (Women and Infants Hospital/Brown).
2) In Methods, you note appropriately that the study was not powered to assess interaction of the two arms in the SUPPORT study (sat target vs CPAP/surfactant). In Neil's manuscript, however, he reported in the last paragraph of the Discussion that 'While the study was not powered to detect an interaction between the two interventions, we did propsectively agree to evaluate such interactions and none were found'. A similar statement in your manuscript may be useful as well as make the two manuscripts consistent.
3) It is unfortunate that the causes of death are unavailable to assess the biologic plausibility of hypoxia as a contributing factor re: the significant difference between the high and low targeted SpO2 groups.
4) Abstract, background, line 1: Should it be 'the incidence of threshold prematurity'?
5) Abstract, background, line 2: 'Oxygenation levels lower than previously maintained' may be less clear to the reader than 'oxygenation targets lower than previously employed' (or something similar).
6) Abstract/methods: Would it be clearer to make the second half of the composite outcome 'death before NICU discharge'?
7) Page 10, paragraph 1, line 9: Change 'levels' to 'PaO2'?
8) Page 10, paragraph 2, line 4: Do we need to describe the study population in the survey study by BW or GA, or was it truly all infants cared for in thoe study NICUs?
9) Page 13, line 1: Should we add that randomization occurred at birth and that randomization was implemented in the DR?
10) Page 15, line 4: Per the protocol on the NRN website, it appears that chest compressions and

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epinephrine in the DR were also trcaked as saftey indicators.
11) Page 15, Results paragraph 1: May it be useful to provide a bit more detail about the temporary hold on the study, i.e., the fact that infants not requiring supplemental O2 frequnetly had SpO2s higher than assigned.
12) I agree with Ed Bell's suggestion that it may be useful for the reader to know that the data indicate 1 more death before discharge for every 2.6 less cases of threshold ROP in the low target group.
13) It is probably worth adding to the discussion that the real importance of the difference in threshold ROP re: blindness, other permanent visual disability will be evident only after these functional outcomes are assessed at 18-22 months follow-up.
14) Table 3: The data for the two groups and the P value for the row 'Alive off mechanical ventilation by day 7) are missing.

I hope these are useful. If other thoughts occur before the teleconference on Monday, I will certainly forward them.

Roger

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Saturday, November 07, 2009 5:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu; Gantz, Marie; Nancy Newman; Susie Buchter; Brenda Morris; Laroia, Nirupama; Sood, Beena; sduara@miami.edu; Michael O`Shea; Anthony Piazza; vineet.bhandari@yale.edu; Vivek.Narendran@cchmc.org; Phelps, Dale; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley Yoder; Brenda Poindexter; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

The O2 sat paper went out without figures due to some computer glitch. Here is a copy with the 2 figures.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 3:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi

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Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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From: Wally Carlo, M.D.
To: Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: O2 Saturation Manuscript
Date: Monday, November 09, 2009 2:10:49 PM

THANKS.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, November 06, 2009 6:13 PM
To: Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: O2 Saturation Manuscript

See below for some answers (in green). Others I'm still working on. New tables 1, 2, and 3 are attached, as are tables for cause of death (Table 1 and COD table have unadjusted p-values, all other p-values for outcomes are adjusted). Note that the DSMC was concerned about the "other" COD category. These are mostly cases where a terminal event rather than an underlying cause of death was recorded on the GDB forms. We may have to query the centers to obtain more information. See the end of the COD document attached for "other" causes that have been moved into other categories, as well as those that are still in the "other" category of the table. Please let me know if any adjustments to these categories need to be made. I have not updated any numbers in the text of Wally's paper yet, but I'll work on that and the other outstanding issues this weekend.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

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From: Das, Abhik
Sent: Friday, November 06, 2009 4:45 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E];
nfiner@ucsd.edu; Gantz, Marie
Subject: RE: O2 Saturation Manuscript

I have no problem with including that figure in a supplemental appendix.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Gantz, Marie;
Das, Abhik
Cc: Wally Carlo, M.D.
Subject: RE: O2 Saturation Manuscript

Dear Rose, Neil, Marie and Abhik:

I have enclosed responses to Rose's comment below (red). I also incorporated Abhik's.

Abhik and Marie:

There are a few requests for you.

Thanks Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 11:23 AM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'mgantz@rti.org'; 'adas@rti.org'
Cc: 'mcunningham@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'petrie@rti.org'
Subject: Re: Manuscript

Wally

Thanks for quickly turning this around.

We refer ro nonrandomized studies in several sections of the paper. Is observational a better word?

Sometimes "observational" may be ok but most studies were pre post studies (following a change in oxygen saturation targeting). These studies could be called "controlled" which is a better level of evidence than observational. I have been more specific in how I refer to those studies in the revised draft.

There is no citation of the STOP-ROP paper in the manuscript. Although this looked at saturation levels in pretheshold ROP, it should probably be listed.

It was quoted (ref 20) but the incorrect reference was put inadvertently in the reference list. This is now corrected. If we are below the NEJM word limit, I can add more details (especially that the intervention was late in the hospital course).

Methods - end of the first paragraph - delete "before delivery" as part of the consent process. Although this occrred in the vast majority, there were a few that occurred after delivery for a variety of reasons.

This happened because the protocol allowed it. I was trying to keep it short so may omit the details (exception).

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Wold it be possible to include the scatter graph of actual versus monitor oximetry levels included in the stdy protocl in the supplementary/appendix materials? We explain this 3 percent offset in the methods on page 12, bt the graph really shows it to those who are visually oriented.

Abhik: What do you think?

At the bottom of page 12 we stated that sat targets were maintained by "clinicians.". It may be more accurate to say adjustments.... were performed by "NICU or clinical staff.". This way, everyone (nrse, md, resp therapist) are included and it is acucrate reporting.

Agree, change made.

In the methods section (page 13) nder assessments - should we (or do we even have space) report abot the 14 day safety monitoring??

Rose: What should I say about the 14 day safety monitoring?

Leave 18-22 month FU out of the methods section on page 13 I this shold be incluuded in the discussion.

Moved to the Discussion section as suggested.

Bottom of page 14 I should we add one sentence about the first dsmc look at the data that occurred due to concern with compliance with sat levels are the part of the investigators as this happened prior to 25 percent enrollment? I suggest "dsmc evaluated sat data upon reqest of investigators to evaluate compliance after enrollment of XX infants.". You do explain this in the results and it leaves the reader wondering why we did this.

Done

Results - first line page 15 I enrollment started in Feb 2005 not Jan 2004 (I think).

Marie: Can you check?

MG: First enrolled infant was in Feb 2005

Discussion - second line - you stated "standard" practice. I recommend

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changing this to "common" practice as there was no AAP guideline or otherwise indicating "standard."

Done

Page 17 - end paragraph- reviewers may want to know abot the lower sat infants and deaths (ron goldberg's comment at the sc meeting.

I think this will need further explanatory analysis. We may be able to address with Kaplan Meier plot and cause of deaths (which I have requested to Marie).

The last paragraph of the discussion should restate the primary outcome and the two significant otcones of ROP and BPD benefit.

Done, except BPD was only decreased when analyzed by O2 weaning, not by physiologic definition and the competing outcome of death eliminated the BPD benefit. Thus, I have not emphasized a BPD benefit.

Table 1 has 655 in low sat group and 661 in high sat group. On table 2 many of the denominators are 654 in low sat group and there is a denominator of 662 on several of the high sat outcomes - we need to fix this.

Marie: Can you correct these? Can you also verify the figure numbers?

Also, threshold rop/death says 17/605 for low sat group (should be 170/) and high sat group says 198.616.

Corrected

Figure 1 - is there a way to have "pregnancies" assessed for eligibility?". That is actually how this nfolded.

Marie: Please check.

MG: We could convert certain numbers to pregnancies, but one of the problems is that those numbers are terrible to begin with. They do not account for pregnancies that were screened but did not result in deliveries that made it into the GDB or SUPPORT. If we want to give readers an accurate picture of how many women were screened/eligible we would be better off citing numbers from the Antenatal Consent study.

For figure 2 - is there any way to "statistically" assess if we reached an adequate separation between the two groups??
Marie: Can you analyze? I am sure they are statistically significant.

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MG: A Rank Sums test of the difference of the medians of the two distributions in Figure 2 has a p-value of <0.0001.

Also -
I also pulled the May 2009 NeoProm confidential update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. I have spoken to NICHD and NHLBI leadership. The other trials are enrolling children following delivery. Our dsmc meets Nov 4 -the leadership would like input from or DSMC prior to any possible confidential dscussions with other dsmc's. Also the observed mortality between the two sat groups (16 and 20 percent) is tighter than the nrn range of mortality from historical data provided to our dsmc (9.5-32 percent deaths by day 14).

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>
Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

Wally Carlo, M.D.

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From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: PAS O2 saturation abstract for NIH clearance
Date: Monday, November 09, 2009 2:00:26 PM
Attachments: randomized o2.docx

Hi Rose and all:

Enclosed is the O2 sat abstract. My title is more specific than Neil's. See which style you all prefer. I am concerned using Neil's because then both would have the same title.

I had to shorten the table as no more data would fit in.

Wally

Wally Carlo, M.D.
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Abstract is at 99.85% of the allowed 2600 characters.
The count includes characters and spaces in the following: Authors, Abstract Title, Abstract Body, Tables and Figures.

Preview Abstract
Draft Preview of Abstract #751587
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First Author: W A Carlo **File Number:** 751587

Presenting Author: W A Carlo

Responsible Author: W A Carlo

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Waldemar A Carlo MD

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---

Responsible Author: W A Carlo, MD

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Responsible Author Declaration:
As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: W A Carlo, MD

Department/Institution/Address: Division of Neonatology, University of Alabama at Birmingham, 619 19TH ST S, NHB 525, Birmingham, Alabama, 35249, United States

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Presenter E-mail: wcarlo@peds.uab.edu

The presenting author is member of these Alliance Societies:

Is Presenting Author a Trainee? No, Not a Trainee

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Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

Awards Applied for:

Consider for PAS Travel Grant Award: No

Sponsoring Member for PAS Abstracts
Sponsored by: Waldemar A Carlo,
Email: wcarlo@peds.uab.edu
Is the Sponsor an Author? Yes
Sponsoring relations:

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American Pediatric Society
Society for Pediatric Research
American Academy of Pediatrics

Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants-the SUPPORT Trial

W A Carlo, MD[1], N N Finer, MD[2] and on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. [1]University of Alabama at Birmingham, Birmingham, Alabama, United States and [2]University of California San Diego, San Diego, California, United States.

Background: Recent non-randomized studies suggest that the incidence of retinopathy of prematurity (ROP) decreases in premature infants with oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce ROP without increasing adverse outcomes

Objective: To test the hypothesis that a lower oxygen saturation target decreases severe ROP and/or death in extremely premature infants.

Design/Methods: 1316 infants of 24 0/7 to 27 6/7 weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters or part of a 2x2 factorial trial. The primary outcome was a composite of severe ROP (Type 1 threshold ROP/surgery/bevacizumab) and/or death.

Results: Severe ROP/death did not differ between the oxygen saturation target groups (Table; adjusted for stratification factors: study center, gestational age group, and familial clustering). Severe ROP was decreased (P<0.001) in the lower oxygen saturation target group but death was more frequent (P=0.045, Table). Oxygen use at 36 weeks significantly decreased in the lower oxygen saturation target group but oxygen use by the physiologic definition or oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups (Table).

Conclusions: Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of severe ROP/death but resulted in an increase in mortality that partially offset a decrease in severe ROP. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term ROP benefits.

	Lower O2 Saturation Group n/N (%)	Higher O2 Saturation Group n/N (%)	Adjusted Relative Risk1 (95% CI)
Severe ROP/death	170/605 (28.3)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe ROP	43/483 (8.9)	95/514 (18.5)	0.51 (0.37, 0.71)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia (physiologic) at 36 weeks	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)

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From: Wally Carlo, M.D.
To: Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 1:55:51 PM

Marie:

GREAT!

You were going to get me data on causes of death. Can you do it?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 12:50 PM
To: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are the paper and source tables in which percentages now have a decimal.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 12:23 PM
To: Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Ok, done

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics

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-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 09, 2009 10:48 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I agree with Marie that we should call it severe ROP or death, and then define severe ROP as threshold ROP or ROP requiring surgery.

Thanks

Abhik

-----Original Message-----
From: Gantz, Marie
Sent: Monday, November 09, 2009 11:45 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole

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subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Cell: 205 266(b) (6)

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org; Roger Faix; Bradley.yoder@hsc.utah.edu; kurt.schibler@cchmc.org; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 12:28:00 PM

Ok with me.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) [redacted]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 11:27 AM
To: 'Finer, Neil'; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; Roger Faix; Brad Yoder (Bradley.yoder@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

Kurt has proposed an alternative for the CPAP/surf paper. As many of you are likely to recall, Ed Donovan organized the SUPPORT training and the video in 2004. Let me know if ED and Vivek can appear on the CPAP/surf paper.

Thanks
Rose

From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, November 09, 2009 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper
Importance: High

Hi Rose,
Personally, I would like to advocate that Ed Donovan and Vivek Narendran both be listed as Cincinnati authors on the CPAP Surfactant manuscript since Ed and Vivek did a lot to move forward the study up front and Vivek was instrumental during the trial. (Ed did a lot with initial start up and education, hosting the training, producing the training video, and was the Cincinnati PI at the beginning of the study). I would like to be listed as the author from Cincinnati on the Oxygen Saturation.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009

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Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736-(b)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
___X__ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
_____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

_____ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

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Hi Wally,

Just wondering,

Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.

Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Wally Carlo, M.D.
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 12:17:36 PM

I have changed the primary outcome to severe ROP/death; that is how it was called in the clinicaltrials.gov record.

Let me know if there are any objections.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 10:45 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole

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subcommittee (see below) .

The paper and the PAS draft are enclosed.

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Cc: Wally Carlo, M.D.
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From: Wally Carlo, M.D.
To: Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 9:41:19 AM

Ok, will use that adjusted.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 09, 2009 8:40 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo, M.D.; wrich@ucsd.edu
Subject: RE: Oxygen Saturation paper for your comments.

We should be consistent and present only the adjusted results for the survival analysis.

Thanks

Abhik

-----Original Message-----
From: Gantz, Marie
Sent: Sunday, November 08, 2009 3:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; 'wrich@ucsd.edu'
Subject: RE: Oxygen Saturation paper for your comments.

Attached is the Oxygen Saturation paper with my edits and comments. I have updated all numbers and p-values. I have added to the methods section on statistical analysis, and I have added the survival analysis. Instead of using Kaplan-Meier analysis I have used Cox regression in order to adjust for stratification and clustering as in the other analyses. The results were similar, although the difference in the survival curves was significant (p=0.045) after adjustment and non-signficant in the KM analysis without the adjustments. See attached for the two survival curves for comparison.

I will also update all numbers in the CPAP paper and send that out as well.

Marie

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Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, November 08, 2009 3:06 PM
To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz, Marie; 'wrich@ucsd.edu'
Cc: 'MSumner@peds.uab.edu'
Subject: Re: Oxygen Saturation paper for your comments.

I think neil and wally on behalf of the support subcommittee of the nichd nrn is fine. If space permits, marie and wade can be added. Limitation in author number was instituted because the authors were taking up to 25 percent of alloted space.
I need the abstract in the next day or so for nichd clearance.
Thanks

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>
Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 13:27:55 2009
Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf On both Abstracts I would like at least you and me as authors and then whatever follows I will put Finer, Carlo, you can do the flip side I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

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Cc: Wally Carlo, M.D.
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Wally

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From: Wally Carlo, M.D.
To: Das, Abhik; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 9:38:26 AM

Neil:

I agree with Abhik that we should soften the results that are related to the exploratory subgroup analyses. In many ways, our work sets standards for our field and is held to the highest scrutiny.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 09, 2009 8:27 AM
To: Finer, Neil
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: Oxygen Saturation paper for your comments.

Neil:

Some suggested editorial changes are attached, that cuts down on the words a little bit. I have expressed my reservations about the boldness of the conclusion before; so I won't repeat that again! I can live with it if it is acceptable to the subcommittee and the steering committee.

Thanks

Abhik

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, November 08, 2009 11:26 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Hi Neil:

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Here are a few suggestions on the abstract.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 9:48 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I do not think that the abstracts will fit if we add all the subcommittee members - I am at 100.7% with this version Please review
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, November 08, 2009 2:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Should we try to put the whole subcommittee?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, November 08, 2009 4:22 PM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'adas@rti.org'; 'mgantz@rti.org'; 'wrich@ucsd.edu'
Cc: Marsha Sumner
Subject: Re: Oxygen Saturation paper for your comments.

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If you can fit more authors, it is fine

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>
Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 17:18:45 2009
Subject: RE: Oxygen Saturation paper for your comments.

Hi Neil:

That sounds fine to me. Usually we have not put too many authors. We can put you and me and then "and the SUPPORT Subcommittee of the NICHD Neonatal Research Network".

Rose:

OK?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Cc: Marsha Sumner
Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf On both Abstracts I would like at least you and me as authors and then whatever follows I will put Finer, Carlo, you can do the flip side I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade
Cc: Marsha Sumner

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From: Phelps, Dale
To: Wally Carlo, M.D.; Finer, Neil
Cc: Das, Abhik; Gantz, Marie; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Comments on manuscript
Date: Monday, November 09, 2009 9:30:20 PM
Attachments: Oxygen Saturation Target 11 6 09 Phelps.edits..doc

---

Hi Wally,
Here are my tracked changes edits, questions, suggestions on the Saturation paper.

I'm generally feeling like we have not done enough examination of the data to feel comfortable with the conclusions (although I don't really think they will change.) I realize you are busy working on that remedy.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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Edits: Phelps: ~~11/06~~11/09/09
7.0

[editorical comments and/or questions are in square brackets, and BOLD.]

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; **[Faix and Yoder are both listed under Brown in the second listing.... however, here, they are listed at Utah and Brown respectively. Is this correct?]** Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study: **[Because you say 'in addition to those listed as authors' , you need to remove those already listed as authors from the Boiler Plate below. dlp]**

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; [redacted] Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; [redacted] while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; [redacted] **[We may wish to put the NNT comments in here.--dlp]**

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity was reduced when conventional~~increased with~~ exposure to prolonged ~~unrestricted~~ oxygen in premature infants was restricted in randomized controlled trials performed in the 1950s.[1] **[This is a little iffy, referencing a review instead of the original papers, but it may be ok this far out. It is not appropriate to call the 1956 Kinsey trial "unrestricted oxygen" because they gave FiO2 0.50 carefully for 4 weeks (conventional treatment). ~~We need to address it otherwise.~~ --dlp]** However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter prospective observational study [13] could not determine an association between oxygen levels and retinopathy, a single center randomzied trial~~cohort study~~ using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels ≥ 80 mmHg in a secondary analysis.[14]

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Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation over ≥ 92% as compared to below 92% (3.3 ± 0.3 versus 1.4 ± 0.2%), or greater

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than ~~≥~~ 98% satiration, compared to less than 98%~~-~~ (5.6 ± 1.1 versus 3.1 ± 0.3%).[5] **]Wally, I could not figure out what the sentence said for sure, but I think this is what you meant. Did I get it right? dlp]** The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

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We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to compare two different respiratory support strategies~~control for the ventilatory approach and test other hypotheses~~ and will be reported separately.

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METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those with major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with an output display of 88 to 92% for these oxygen ranges, with an offset of plus 3%, or minus 3% from the display (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in older premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% ~~and~~ or 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. **JI do**

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not understand what this last phrase about the alarms is saying... did alarms go off at 85% saturation and 95% saturation? or did the protocol recommend that centers set the alarms at these levels?] Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2 factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. ROP examinations were conducted according to published guidelines (AAP/AAO joint statement, ref xx added to references) until the study endpoint or resolution was reached. The unfavorable study endpoint was threshold ROP as described below in at least one eye. Resolution was defined as a fully vascularized retina, or immature vessels or regressing ROP in zone III for two consecutive examinations in each eye. The primary outcome was death before discharge and/or threshold retinopathy. Threshold ROP~~retinopathy of prematurity~~ (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative

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Group[18]) was coded if any of the following findings were present. ~~up to 55 weeks post-menstrual age:~~

[Note correction of reference # 18. this is the wrong one.~~8. this is the wrong one~~]

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following for ROP: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, ~~and~~ or bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months

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corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms. **[Although it may not have been powered for this, why have we not looked to see if an interaction is apparent? dlp?]**

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Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment [redacted] to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

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RESULTS

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1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Survival data was known for all enrollees to discharge, and ROP outcomes among survivors was obtained in 92%. Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1). **[I would add to this table the n, percent for each saturation group that went into the CPAP arm. (or if you prefer the prophylactic surfactant arm. This is a baseline characteristic for these infants. --dlp]**

[Dr. Guillet from Rochester notes: I don't know if it is statistically significant, but the low sat group got more surfactant (baseline demographic table). Could the randomization to CPAP vs. early surfactant have confounded the high/low saturation results (or, I guess, vice versa)? -dlp]

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge (retinopathy/death), did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; [redacted] Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated [redacted] **[We have not seen Figure 2 yet]** Mortality

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in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). **[I made a new paragraph--dlp]**

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Threshold retinopathy was decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p[redacted] **[We have to look at some other things here. Can't be left at one sentence ?? How about looking at the data to see if this sentence (entirely invented by me just now) is true? Those infants who developed threshold ROP as compared to those that did not were of younger GA, lower birthweight, where more often male, and White, but were similar when compared across the two saturation target groups... It would be quite interesting if these know ROP related characteristics were different across the saturation groups among those with the unfavorable outcome. --dlp]** Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

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The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). **[There is no comment here about this figure. and no legend. You have to at least say if the figure is data while infants were receiveing supplemental oxygen, or if the figure represents all saturation data, even when they are on room air. --- too incomplete. --dlp]** These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal

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synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization also did not differ ~~as well~~.

[I concur with Ed Bell's additional analyses giving NNT for both ROP reduction and NNH for death. Please incorporate. -- Alternatively, you could put it in the discussion after the first paragraph which would be a great lead in for it. dlp]

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DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming a~~the~~ common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease ~~retinopathy of prematurity~~ROP. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold ROP~~retinopathy~~, it also increased ~~the risk for~~ mortality.

This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. **[Isn't this first sentence incorrect? and if not incorrect, isn't it irrelevant? The significant difference was observed.]** ~~However, t~~This is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher or lower susceptibility to the effects of lower oxygen

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saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials.**[you had better reference the source of this statement or get ready to explain at lot.]** It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], **[why not reference the original paper instead of this review? -- reference provided in reference list for you Kinsey 1956]]** which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

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[This would be a good place to discuss the observation that the difference in mortality occurred after the first couple of weeks. Why would that be? You may have permission to speculate here... Fetal hemaglobin works better with low saturations? and as they get older adult hemaglobin levels go up? (maybe from transfusions). Or ..... other theories? --dlp]

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Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation groups which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other published randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces severe ROP~~retinopathy of prematurity~~. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not significantly affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across **[around?]** the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. **[While the following sentence is true, I don't know if it will be counterproductive or helpful to have it in the paper. I would be inclined not to use it. Instead empahsize the need for NDI. --dlp]** At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)
Randomized into the CPAP factorial arm	xxx/xxx (xx%)	xxx/xxx (xx%)

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Table 2. Major Outcomes

~~Predischarge~~ Clinical outcomes – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy and or~~/d~~ death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD	data are missing	data are	missing

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[There are no legends for the figures. These need to be written.]

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Figure 1

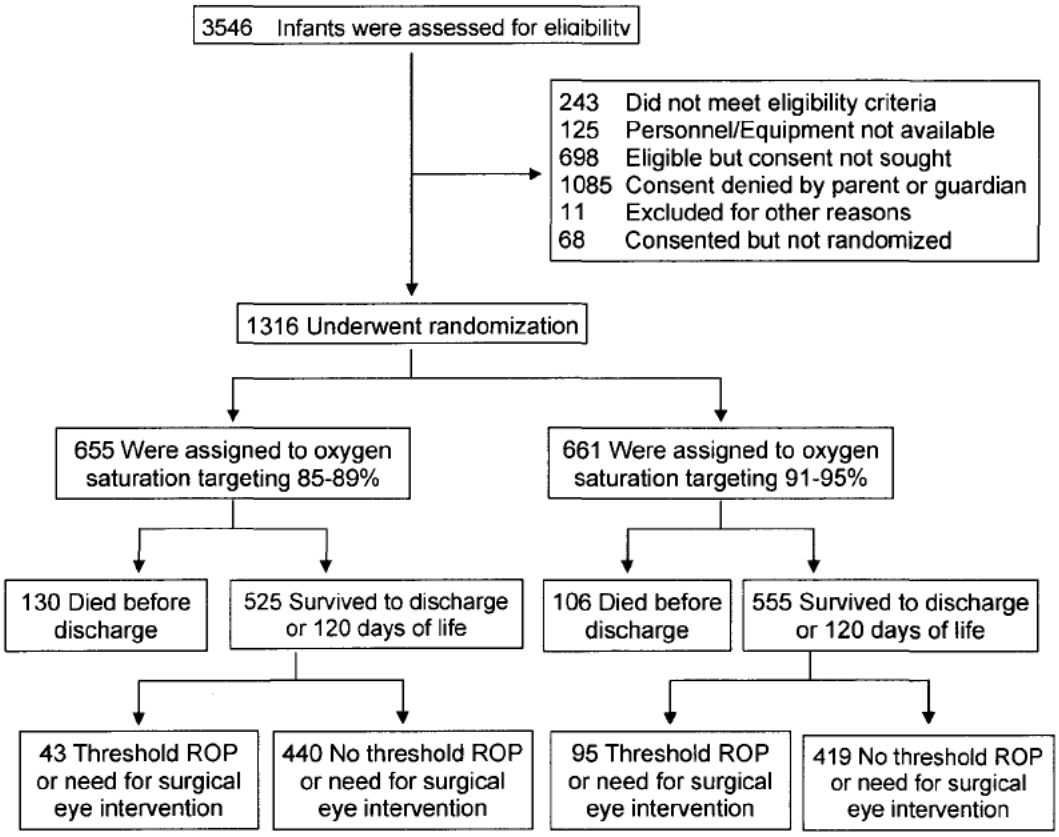

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Figure 2 Kaplan Meier plot for mortality (from Marie)

[Figure does not appear in my print out…. do we have this yet? --dlp]

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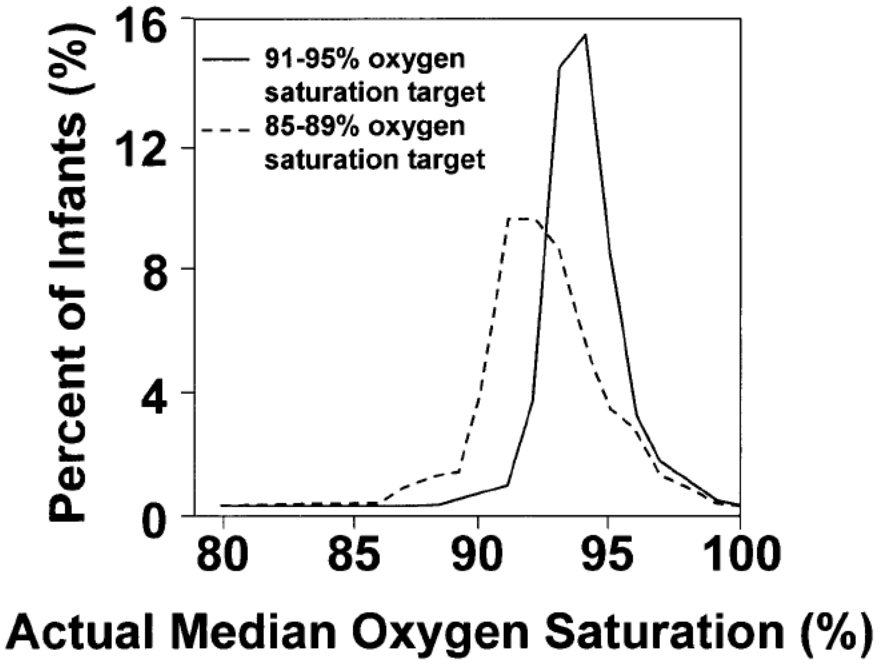
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to to the conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 9:26:32 AM

Rose:

Rochester only contributed 8 patients so only one author.

Kurt on both.

See below

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 8:22 AM
To: 'Finer, Neil'; 'wrich@ucsd.edu'; mcw3@case.edu; wacarlo@uab.edu; Roger Faix; alaptook@WIHRI.org; Kurt Schibler [kurt.schibler@cchmc.org]; 'Nancy Newman'; Gantz, Marie; 'Das, Abhik'; Brad Yoder (Bradley.yoder@hsc.utah.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
_____ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
___x__ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

__x___ Kurt for both papers
_____ Kurt for only saturation paper

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,
Just wondering,
Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.
Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
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Gualala, CA 95445
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From: Gantz, Marie
To: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: PMA at final ROP status
Date: Monday, November 09, 2009 5:29:18 PM
Attachments: PMA at Final ROP Status- Graphs - 09NOV09.doc
PMA at final ROP status - 09NOV09.doc

Attached is information on the PMA of SUPPORT infants at the time they reached final ROP status. For all infants who met criteria for severe ROP, final ROP status was obtained by 53 weeks PMA, and the previous ROP exam was within three weeks of the final exam.

For infants who met criteria for final ROP status and did not have severe ROP, final ROP status was obtained by 55 weeks PMA for 91%. For 64% of those who did not have severe ROP, final status was obtained within 3 weeks of the previous exam, and for all but two infants, the exam previous to the one in which final ROP status was obtained was at <=55 weeks PMA. However, there were some cases where a lot more time passed between exams and where final status was obtained well after 55 weeks PMA, as you can see in the attached frequencies and graphs.

Marie

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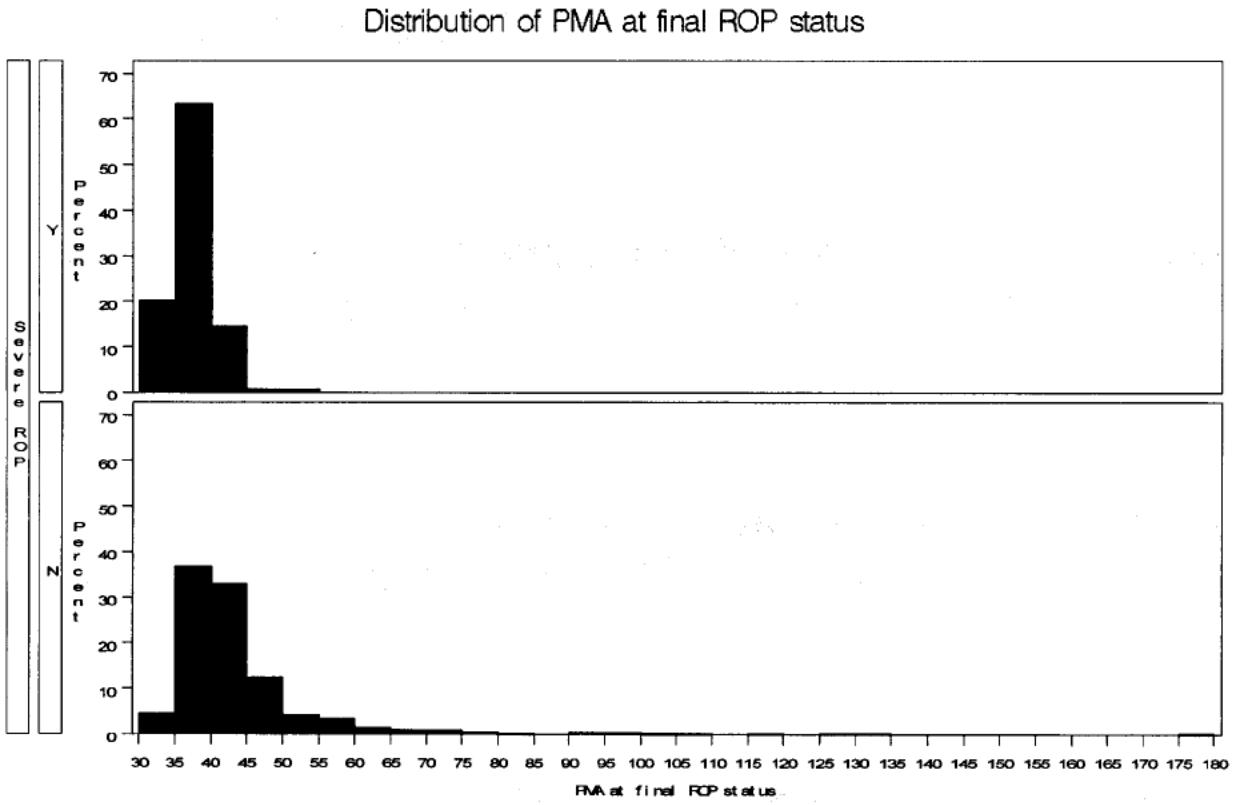
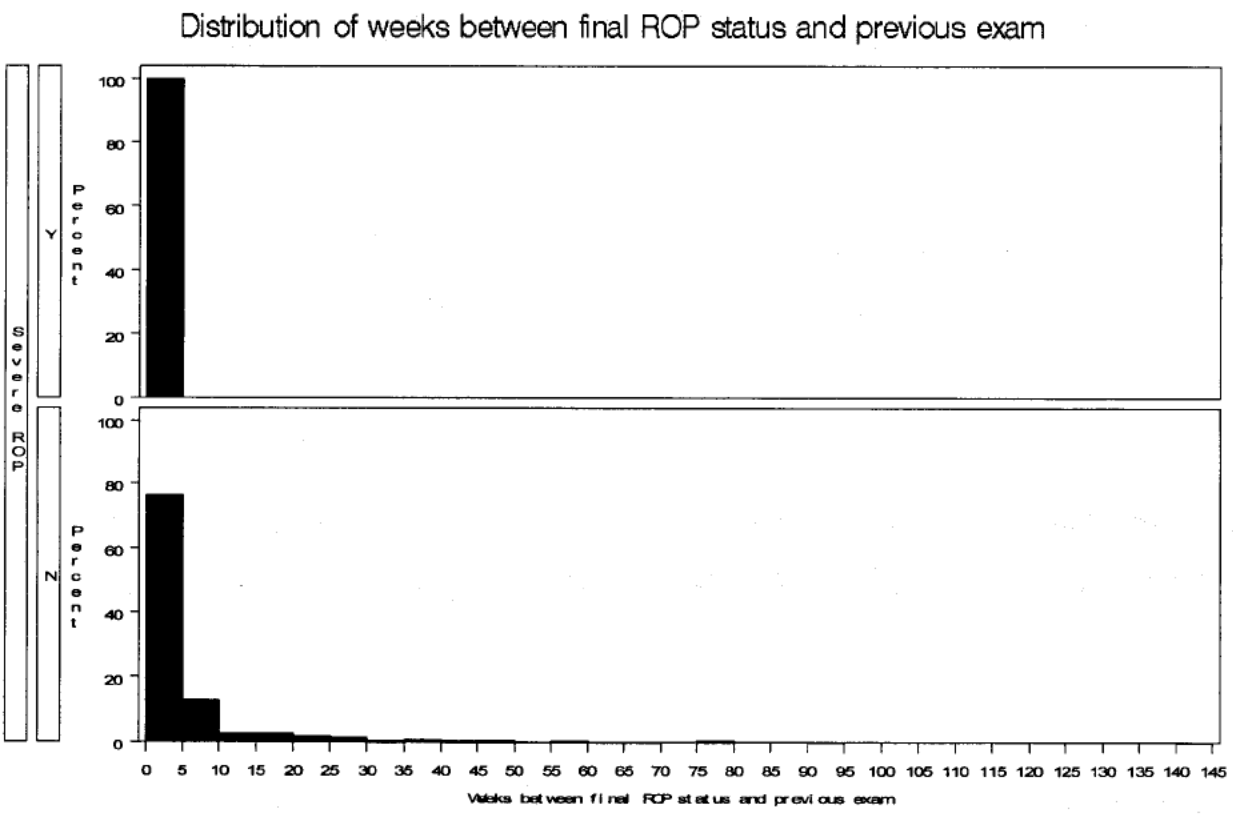
PMA at Final ROP Status – Graphs – 09NOV09





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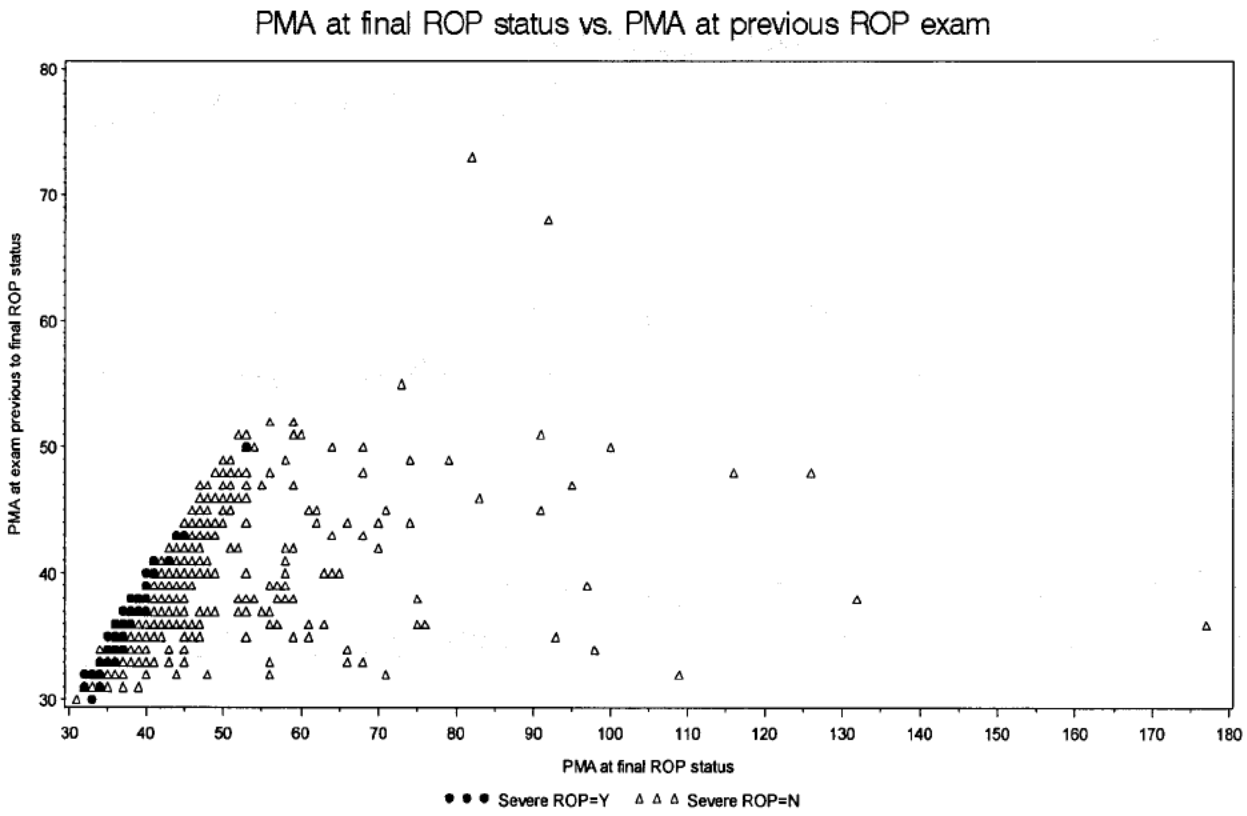

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The FREQ Procedure

Severe ROP=Y

PMA at final ROP status				
roppma	Frequency	Percent	Cumulative Frequency	Cumulative Percent
32	3	2.19	3	2.19
33	6	4.38	9	6.57
34	19	13.87	28	20.44
35	31	22.63	59	43.07
36	22	16.06	81	59.12
37	18	13.14	99	72.26
38	7	5.11	106	77.37
39	9	6.57	115	83.94
40	11	8.03	126	91.97
41	3	2.19	129	94.16
43	2	1.46	131	95.62
44	4	2.92	135	98.54
45	1	0.73	136	99.27
53	1	0.73	137	100.00

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The FREQ Procedure

Severe ROP=N

	PMA at final ROP status			
roppma	Frequency	Percent	Cumulative Frequency	Cumulative Percent
31	2	0.23	2	0.23
32	4	0.47	6	0.70
33	12	1.40	18	2.10
34	21	2.44	39	4.54
35	38	4.42	77	8.96
36	55	6.40	132	15.37
37	67	7.80	199	23.17
38	69	8.03	268	31.20
39	88	10.24	356	41.44
40	76	8.85	432	50.29
41	77	8.96	509	59.25
42	50	5.82	559	65.08
43	48	5.59	607	70.66
44	32	3.73	639	74.39
45	38	4.42	677	78.81
46	24	2.79	701	81.61
47	22	2.56	723	84.17
48	14	1.63	737	85.80
49	9	1.05	746	86.85
50	8	0.93	754	87.78
51	7	0.81	761	88.59
52	8	0.93	769	89.52
53	12	1.40	781	90.92
54	2	0.23	783	91.15
55	2	0.23	785	91.39
56	10	1.16	795	92.55
57	4	0.47	799	93.02
58	7	0.81	806	93.83
59	6	0.70	812	94.53
60	1	0.12	813	94.64
61	4	0.47	817	95.11
62	2	0.23	819	95.34
63	2	0.23	821	95.58
64	3	0.35	824	95.93
65	1	0.12	825	96.04
66	3	0.35	828	96.39
68	4	0.47	832	96.86

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The FREQ Procedure

Severe ROP=N

PMA at final ROP status				
roppma	Frequency	Percent	Cumulative Frequency	Cumulative Percent
70	3	0.35	835	97.21
71	2	0.23	837	97.44
73	1	0.12	838	97.56
77	2	0.23	840	97.79
78	2	0.23	842	98.02
78	1	0.12	843	98.14
79	1	0.12	844	98.25
82	1	0.12	845	98.37
83	1	0.12	846	98.49
91	2	0.23	848	98.72
92	1	0.12	849	98.84
93	1	0.12	850	98.95
95	1	0.12	851	99.07
97	1	0.12	852	99.19
98	1	0.12	853	99.30
100	1	0.12	854	99.42
109	1	0.12	855	99.53
116	1	0.12	856	99.65
126	1	0.12	857	99.77
132	1	0.12	858	99.88
177	1	0.12	859	100.00

Frequency Missing = 1

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The FREQ Procedure

Severe ROP=Y

PMA at exam previous to final ROP status				
prevpma	Frequency	Percent	Cumulative Frequency	Cumulative Percent
30	1	0.74	1	0.74
31	2	1.47	3	2.21
32	10	7.35	13	9.56
33	17	12.50	30	22.06
34	26	19.12	56	41.18
35	24	17.65	80	58.82
36	16	11.76	96	70.59
37	9	6.62	105	77.21
38	11	8.09	116	85.29
39	8	5.88	124	91.18
40	3	2.21	127	93.38
41	3	2.21	130	95.59
43	5	3.68	135	99.26
50	1	0.74	136	100.00

Frequency Missing = 1

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The FREQ Procedure

Severe ROP=N

PMA at exam previous to final ROP status				
prevpma	Frequency	Percent	Cumulative Frequency	Cumulative Percent
30	1	0.12	1	0.12
31	20	2.34	21	2.46
32	50	5.85	71	8.31
33	46	5.39	117	13.70
34	83	9.72	200	23.42
35	84	9.84	284	33.26
36	96	11.24	380	44.50
37	87	10.19	467	54.68
38	74	8.67	541	63.35
39	72	8.43	613	71.78
40	55	6.44	668	78.22
41	40	4.68	708	82.90
42	29	3.40	737	86.30
43	25	2.93	762	89.23
44	21	2.46	783	91.69
45	17	1.99	800	93.68
46	10	1.17	810	94.85
47	11	1.29	821	96.14
48	13	1.52	834	97.66
49	5	0.59	839	98.24
50	5	0.59	844	98.83
61	5	0.59	849	99.41
62	2	0.23	851	99.65
65	1	0.12	852	99.77
68	1	0.12	853	99.88
73	1	0.12	854	100.00

Frequency Missing = 6

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The FREQ Procedure

Severe ROP=Y

Weeks between final ROP status and previous exam				
pmadiff	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	18	13.24	18	13.24
1	96	70.59	114	83.82
2	16	11.76	130	95.59
3	6	4.41	136	100.00

Frequency Missing = 1

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The FREQ Procedure

Severe ROP=N

Weeks between final ROP status and previous exam				
pnt diff	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4	0.47	4	0.47
1	66	7.73	70	8.20
2	284	33.26	354	41.45
3	196	22.95	550	64.40
4	101	11.83	651	76.23
5	49	5.74	700	81.97
6	29	3.40	729	85.36
7	13	1.52	742	86.89
8	10	1.17	752	88.06
9	9	1.05	761	89.11
10	6	0.70	767	89.81
11	5	0.59	772	90.40
12	8	0.94	780	91.33
13	1	0.12	781	91.45
14	2	0.23	783	91.69
15	2	0.23	785	91.92
16	6	0.70	791	92.62
17	4	0.47	795	93.09
18	7	0.82	802	93.91
19	4	0.47	806	94.38
20	4	0.47	810	94.85
21	4	0.47	814	95.32
22	1	0.12	815	95.43
23	2	0.23	817	95.67
24	4	0.47	821	96.14
25	5	0.59	826	96.72
26	4	0.47	830	97.19
27	1	0.12	831	97.31
28	1	0.12	832	97.42
30	2	0.23	834	97.66
32	1	0.12	835	97.78
33	1	0.12	836	97.89
35	1	0.12	837	98.01
37	2	0.23	839	98.24
39	2	0.23	841	98.48
40	2	0.23	843	98.71
46	1	0.12	844	98.83

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The FREQ Procedure

Severe ROP=N

Weeks between final ROP status and previous exam				
pmadiff	Frequency	Percent	Cumulative Frequency	Cumulative Percent
48	1	0.12	845	98.95
50	1	0.12	846	99.06
68	2	0.23	848	99.30
84	1	0.12	849	99.41
88	1	0.12	850	99.53
77	1	0.12	851	99.65
78	1	0.12	852	99.77
94	1	0.12	853	99.88
141	1	0.12	854	100.00

Frequency Missing = 6

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From: Wally Carlo, M.D.
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance
Date: Monday, November 09, 2009 4:37:11 PM

I think in the paper we can give the time limit.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 1:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance

Do we need to draw any distinction between this "death" outcome and the death we will report as of the 18 month FU? There are a few infants who died before FU that are not counted as deaths here, and I'm sure there will be more.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 2:40 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance

How about if I just change it to death? OK?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building

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Birmingham, AL 35233-7335
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Cell: 205 266 (b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 1:25 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance

I corrected a couple of typos in the abstract (attached). Also, I wonder if it will be confusing to refer to "oxygen use" in the text but BPD in the table? Finally, we are referring to "death before discharge" in the abstracts and manuscripts, but two of the deaths are cases that were actually "discharged home to die" per the center. It's a small distinction that might not merit any rephrasing of the outcome, but I just wanted to point it out. The two deaths are recorded on the NG03.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 2:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: PAS O2 saturation abstract for NIH clearance

Hi Rose and all:

Enclosed is the O2 sat abstract. My title is more specific than Neil's. See which style you all prefer. I am concerned using Neil's because then both would have the same title.

I had to shorten the table as no more data would fit in.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Phone: 205 934 4680
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Cell: 205 266 (b) (6)

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Monday, November 09, 2009 3:58:23 PM

Thanks.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 3:36 PM
To: Gantz, Marie
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

He is done with his review

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 3:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; aaf2@po.cwru.edu
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Are these figures still needed? I know Neil sent a revision out after Rose's email to me, so please let me know if there is still an issue.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 07, 2009 7:00 AM
To: Gantz, Marie; 'aaf2@po.cwru.edu'
Subject: Fw: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Marie
Can you send Av the figures in a readable format??

From: Fanaroff, Avroy <Avroy.Fanaroff@UHhospitals.org>

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To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Nov 07 00:13:50 2009
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Rose
I will try
I am heading to Florida on the 11th
By the way I am unable to open the figures and tables - please resend
The ROP/Mortality findings are intriguuing
almost like the 50's when restricted oxygen reduced retinopathy but increased mortality
The follow up will be even more rvealing, especially if the low sat group have more problems - or did the low sats weed out the weak?
Be well
Av
PS Note still burning the candle at both ends

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 11/6/2009 4:45 PM
To: Ed Donovan; Fanaroff, Avroy; Stevenson David (E-mail); jon.e.tyson@uth.tmc.edu
Cc: Wally; nfiner@ucsd.edu
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,
You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

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This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

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From: Gantz, Marie
To: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 3:09:14 PM
Attachments: Cause of Death - 09NOV09.doc

Here are the causes of death in both treatment arms, now with decimals on the percentages. If anyone sees a need to reclassify any of the "other" causes specified (listed at the end of the document with my current classification) please let me know.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 1:56 PM
To: Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Marie:

GREAT!

You were going to get me data on causes of death. Can you do it?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 12:50 PM
To: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

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Here are the paper and source tables in which percentages now have a decimal.

Marie

Marie Gantz, Ph.D.
Research Statistician
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828-254-6255
-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 12:23 PM
To: Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Ok, done

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 09, 2009 10:48 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I agree with Marie that we should call it severe ROP or death, and then define severe ROP as threshold ROP or ROP requiring surgery.

Thanks

Abhik

-----Original Message-----
From: Gantz, Marie
Sent: Monday, November 09, 2009 11:45 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our

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infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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Variable	Category	CPAP (N=109)	Surfactant (N=128)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	22/109 (20.2)	40/128 (31.3)	0.2139
	2=BPD	12/109 (11.0)	12/128 (9.4)	
	3=Infection	26/109 (23.9)	20/128 (15.6)	
	4=NEC	14/109 (12.8)	23/128 (18.0)	
	5=CNS Insult	13/109 (11.9)	8/128 (6.3)	
	6=Immaturity	4/109 (3.7)	6/128 (4.7)	
	7=Other	18/109 (16.5)	19/128 (14.8)	

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Cause of Death for CPAP vs. Surfactant
Where GA is 24-25 weeks

Variable	Category	CPAP (N=68)	Surfactant (N=90)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	13/68 (19.1)	31/90 (34.4)	0.1212
	2=BPD	10/68 (14.7)	7/90 (7.8)	
	3=Infection	14/68 (20.6)	15/90 (16.7)	
	4=NEC	10/68 (14.7)	16/90 (17.8)	
	5=CNS Insult	11/68 (16.2)	5/90 (5.6)	
	6=Immaturity	3/68 (4.4)	5/90 (5.6)	
	7=Other	7/68 (10.3)	11/90 (12.2)	

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Cause of Death for CPAP vs. Surfactant
Where GA is 26-27 weeks

Variable	Category	CPAP (N=41)	Surfactant (N=38)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	9/41 (22.0)	9/38 (23.7)	0.4750
	2=BPD	2/41 (4.9)	5/38 (13.2)	
	3=Infection	12/41 (29.3)	5/38 (13.2)	
	4=NEC	4/41 (9.8)	7/38 (18.4)	
	5=CNS Insult	2/41 (4.9)	3/38 (7.9)	
	6=Immaturity	1/41 (2.4)	1/38 (2.6)	
	7=Other	11/41 (26.8)	8/38 (21.1)	

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Variable	Category	Low SpO2 (N=130)	High SpO2 (N=107)	Unadjusted P-Value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	31/130 (23.8)	31/107 (29.0)	0.8018
	2=BPD	14/130 (10.8)	10/107 (9.3)	
	3=Infection	25/130 (19.2)	21/107 (19.6)	
	4=NEC	23/130 (17.7)	14/107 (13.1)	
	5=CNS Insult	12/130 (9.2)	9/107 (8.4)	
	6=Immaturity	7/130 (5.4)	3/107 (2.8)	
	7=Other	18/130 (13.8)	19/107 (17.8)	

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Cause of Death for Low vs. High SpO2
Where GA is 24-25 weeks

Variable	Category	Low SpO2 (N=85)	High SpO2 (N=73)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	23/85 (27.1)	21/73 (28.8)	0.4764
	2=BPD	8/85 (9.4)	9/73 (12.3)	
	3=Infection	16/85 (18.8)	13/73 (17.8)	
	4=NEC	17/85 (20.0)	9/73 (12.3)	
	5=CNS Insult	10/85 (11.8)	6/73 (8.2)	
	6=Immaturity	5/85 (5.9)	3/73 (4.1)	
	7=Other	6/85 (7.1)	12/73 (16.4)	

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Cause of Death for Low vs. High SpO2
Where GA is 26-27 weeks

Variable	Category	Low SpO2 (N=45)	High SpO2 (N=34)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	8/45 (17.8)	10/34 (29.4)	0.4182
	2=BPD	6/45 (13.3)	1/34 (2.9)	
	3=Infection	9/45 (20.0)	8/34 (23.5)	
	4=NEC	6/45 (13.3)	5/34 (14.7)	
	5=CNS Insult	2/45 (4.4)	3/34 (8.8)	
	6=Immaturity	2/45 (4.4)	0/34 (0.0)	
	7=Other	12/45 (26.7)	7/34 (20.6)	

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Contributory cause of death (NG03e, NG03, NG05)=1=RDS

Obs	Other COD specified on NG03e, NG03 or NG05
1	extreme prematurity, RDS, suspected sepsis

Contributory cause of death (NG03e, NG03, NG05)=2=BPD

Obs	Other COD specified on NG03e, NG03 or NG05
2	bpd with multi-systaem organ failure,developed abd. compartment syndrome post-op stricture repair
3	Early onset sepsis & BPD w/severe intracranial hemorrhage.
4	PAHN, Liver Failure, CLD, Resp Failure
5	Endocarditis, Staph pneumonia, multiple pneumothoraces, cystic abscess in lung and advanced BPD
6	Cardiopulmonary arrest due to Pulmonary hypertension & Systemic hypotension & chronic lung disease

Contributory cause of death (NG03e, NG03, NG05)=3=Infection

Obs	Other COD specified on NG03e, NG03 or NG05
7	disseminated Candidiasis
8	pneumonia, sepsis (Blood and lung cultures (+) for S. Aureus, E. Cloacae)
9	proven NEC, sepsis, extreme prematurity
10	extreme prematurity, suspected pulmonary hypoplasia, pneumonia, presumed sepsis
11	ELBW, acute renal failure, severe lung disease, pneumonia, proven sepsis, hypocalcemia
12	septic shock, cardio-respiratory failure, renal failure
13	extreme prematurity, and sepsis
14	extreme prematurity, ecoli sepsis,meningitis
15	Pseudomonas sepsis, acute resp. failure, renal failure
16	pulmonary hypoplasia, clinical sepsis
17	suspected sepsis, DIC, and cerebellar hemorrhage
18	bilateral chylothoraces, sepsis, meconium peritonitis

Contributory cause of death (NG03e, NG03, NG05)=5=CNS Insult

Obs	Other COD specified on NG03e, NG03 or NG05
19	Severe IVH, Pulmonary hemorrhage, HMD, PIE
20	Severe IVH and Pulmonary Hemorrhage
21	Pulmonary hypoplasia with severe intraparenchymal IVH
22	Renal failure and Intraventricular hemorrhage

Contributory cause of death (NG03e, NG03, NG05)=6=Immaturity

Obs	Other COD specified on NG03e, NG03 or NG05
23	severe IUGR
24	prematurity, pulmonary hypertension,cardiorespiratory failure
25	extreme prematurity, severe pulmonary insufficiency

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"Other" causes of death specified by current classification in COD table

Contributory cause of death (NG03e, NG03, NG05)=7=Other

Obs	Other COD specified on NG03e, NG03 or NG05
26	extensive hemorrhage mid brain,brain stem,thalamic with uncal herniation and hydrocephaly
27	Respiratory failure
28	Pulmonary hemorrhage
29	liver failure
30	renal failure; DIC
31	liver failure with bleeding; ost. sites
32	PPHN-persistent pulmonary hypertension of neonate
33	intravascular hemorrhage before birth
34	per autopsy cause is exsanguination
35	pulmonary hypertension, pulmonary hypoplasia
36	pulmonary hypoplasia, chroramnionitis
37	Pulmonary Hypoplasia
38	twin to twin transfusion syndrome
39	massive pulmonary hemorrhage
40	pulmonary hemorrhage
41	pulmonary hypoplasia
42	Lung hypoplasia
43	hypoplastic lung syndrome due to pprom
44	Massive pulmonary hemorrhage without RDS
45	pulmonary hypoplasia due to multiple congenital anomalies
46	MULTI SYSTEM ORGAN FAILURE
47	severe hypoplastic lungs
48	renal failure;
49	severe pulmonary hypertension
50	tetralogy of fallot 7 other multiple cardiac anomalies renal anomalies(possiblby va cterl syndrome
51	cardiac arrythmia
52	extensive hemorrhage of rt. chest cavity after chest tube placement
53	perforation of right atrium by tip of PICC line
54	transposition of the great vessels
55	PREMATURITY, PULMONARY HYPOPLESIA, EXOPHAGEAL ATRESIA, SKELETAL ANNOMALIES
56	probable pulmonary hypoplasia

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From: Gantz, Marie
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts
Date: Monday, November 09, 2009 2:54:51 PM
Attachments: SUPPORT CPAP Manuscript - Network Version Word Nov 6 09_MG2.doc
Tables Nov 09 09 (MG).docx
T2 Other Outcomes - 09NOV09.doc
T1 Patient Description - 09NOV09.doc
T3 BPD Outcomes - 09NOV09.doc

Neil,

Here are the paper and source tables with decimals added to the percentages.

Marie

Marie Gantz, Ph.D.
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-----Original Message-----
From: Gantz, Marie
Sent: Sunday, November 08, 2009 9:36 PM
To: 'Finer, Neil'; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts

Neil,

Here is your paper with updated numbers and my edits, as well as the three source tables I have produced before, now with adjusted p-values and RRs where appropriate.

Will there also be a table showing the primary outcomes? Right now the variables covered in the text and tables don't seem to match completely.

I saw the messages about adding a decimal to the percentages, but not before I had run this version. I will re-run the CPAP and SpO2 paper tables tomorrow with the decimal.

Marie

Marie Gantz, Ph.D.
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 04, 2009 1:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu

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Cc: Das, Abhik; Gantz, Marie
Subject: Re: manuscripts

Hi Rose
Here is the SUPPORT CPAP Surf paper with Tables for circulation
Neil
On 11/4/09 9:33 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

Hi,
Can you send me the updated versions of the manuscripts for distribution to the SC members and co-authors by Monday?? Have you received input from the subcommittee members?

Thanks
Rose

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

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Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Word count:

Abstract: 250

Manuscript: 3079

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were to be intubated and receive ~~d~~ surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while ~~in the NICU and~~ receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was ~~49~~8.7% in the CPAP group versus 54.1% in the surfactant group, (RR 0.91, 95% CI 0.8~~3~~2, 1.0~~1~~0, p=0.07~~2~~6 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (243.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011~~9~~) and fewer required intubation or post natal steroids for BPD, (p<.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP for preterm infants with RDS in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] ~~The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation.~~ Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[14] However, the surfactant trials preceded widespread use of antenatal corticosteroids to promote lung maturation and the placebo groups did not received mechanical ventilation which could be injurious.

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group ~~(9.1~~(9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent

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with the findings of an earlier meta analysies[44], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) ~~with~~) with no statistically significant difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT Trial~~study~~ was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. (already stated)~~These results will be separately reported~~.

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The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 2~~8~~ weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, -and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece ~~resuscitator or~~resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: ~~Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol,~~ CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% for one hour, an arterial $PaCO_2$ > 65 torr ~~documented on a single blood gas within one hour of intubation~~, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU ~~standardpractice~~standard practice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ ~~15 bpm~~15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and ~~be~~ hemodynamically ~~stable with~~stable without

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~~no~~ evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data)~~, and~~, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61~~% using~~% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

Comment [MG1]: I believe the SpO2 paper says 1310. They should agree.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who

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required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1617]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each g~~G~~roup who ~~developed their respective outcome measure of survival~~survived to 36 weeks PMA without BPD ~~at 36 weeks~~. ~~Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering~~ Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age stratum, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

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An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. {Lan-DeMets spending functions with Pocock or {O'Brien-Fleming} boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

Comment [MG2]: Also chest compressions and/or epinephrine in the DR, pulmonary hemorrhage, and nasal breakdown requiring the discontinuation of nasal prongs.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through ~~to Mar 1~~Feb ~~2009 -~~ 2009. Enrollment ~~The trial~~ was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 65.7~~6~~% of the CPAP infants received positive pressure ventilation compared with 92.9~~3~~% of the surfactant infants, and surfactant was given to 14.1% of the CPAP versus 51.4% of the surfactant group; 67.1% of the CPAP infants received surfactant in the delivery room or NICU, compared to 98.9% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34.4% of CPAP infants compared with 93.4% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual~~conceptional~~ age was non-significantly reduced for the CPAP group compared with the Surfactant group, 48.7~~9~~% versus 54.1%, (RR 0.91, 05% CI 0.83~~2~~, 1.01~~0~~, p=0.06~~0~~72) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 43.2% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,~~,~~ 243.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.034, Table 4. Overall, t~~T~~here was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40.2% vs 44.3%, RR 0.94~~3~~, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39.2% vs 40.6~~1~~%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (47.8% vs 51.0%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, ~~nor any differences in~~ length of stay, ~~or~~ days of oxygen for survivors, or discharge on oxygen~~.~~ (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011~~9~~). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. Nearly a~~A~~ll infants in the Surfactant arm were intubated (99.7%), compared with 83.1% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7.2% vs 13.2%, p<0=.00105). ~~The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative~~

Comment [MG3]: Not in table

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~~Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)~~

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants and Hispanic infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 243.9% vs 32.1%, RR=0.74, 95% CI 0.57, 0.98, p=0.034. There was a significantly higher exposure to postnatal steroids for BPD, 20.5% vs 13.0%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[19] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23.3 vs 31.4%, RR=0.75, 95% CI 0.54, 1.05).

Comment [MG7]: Race is not in tab le

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Comment [MG9]: These numbers were reported above but are for the 24-25 week GA stratum

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 10.80% vs 10.21%. The CPAP infants required fewer days of oxygen, ~~40.6~~44.0 vs ~~47.1~~49.5, p=0.035~~1~~, and lesser days of mechanical ventilation, ~~11.3~~13.7 vs ~~14.9~~16.7, p=0.085~~1~~, and fewer infants received postnatal steroids for BPD, 2.9~~3~~% vs ~~8~~7.9%, p=<0.008~~1~~.

Comment [MG10]: Non-significant

Discussion:

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The SUPPORT Ttrial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant ~~given within an hour of life~~ in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention~~other outcome~~ that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[20] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[21]

Our trial~~study~~ differs from the recently reported COIN trial[15~~15~~] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who ~~all~~ were to received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that intent to treat with early CPAP and protocol driven limited ventilator strategy ~~when compared~~compared to ~~with~~ surfactant given within 1 hour of birth was associated with a non-significant decrease in death ~~or survival with~~by 36 weeks PMA or

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BPD as defined by the need for oxygen at 36 weeks from 54.1% to 498.7%. We also noted a ~~very~~ significant 8.2% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.25 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along ~~with reductions~~with reductions in BPD, ~~ROP, significantly,~~ significantly decreased durations of mechanical ventilation ~~and oxygen~~, a decreased need for intubation and exposure to post natal steroids in the overall CPAP ~~group without~~group without any increase in adverse neonatal ~~outcomes represents~~outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks~~, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium~~. We did not find an increase in airleaks in the first 14 days of life with ~~the use of~~randomization to early CPAP at 5 cm H2O compared to ~~the use of~~ early surfactant.

The SUPPORT Trial~~study~~ was a factorial design with each infant randomly ~~receiving 2~~receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were

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adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with ~~the use of~~randomization to surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment~~ed~~ with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death ~~or survival with~~by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks ~~PCA~~ PMA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=6634)	Surfactant (N=6532)	Unadjusted P-value
GA (weeks)	24-25	43.0% (285/663)43% (285/664)	42.9% (280/653)43% (280/652)	0.96860.9932
	26-27	57.0% (378/663)57% (379/664)	57.1% (373/653)57% (372/652)	
Male		51.6% (342/66352% (342/664)	56.7% (370/65357% (370/652)	0.06460.0646
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)38% (255/664)	36.0% (235/653)36% (234/652)	0.3681036841
	Non-Hispanic White	37.7% (250/663)38% (250/664)	41.5% (271/653)42% (271/652)	
	Hispanic	20.8% (138/663)21% (138/664)	18.5% (121/653)19% (121/652)	
	Other/unknown	3.2% (21/663)3% (21/664)	4.0% (26/653)4% (26/652)	
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2834.8 ± 188.2	825.5 ± 198.1825.6 ± 198.3	0.39620.3855
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.126.2 ± 1.1	26.2 ± 1.126.2 ± 1.1	0.64630.6420
Antenatal steroids (any)		96.8% (642/66397% (643/664)	95.6% (623/65296% (622/651)	0.22480.2206
Antenatal steroids (full course)		73.6% (486/66074% (486/661)	69.8% (453/64970% (452/648)	0.12320.1300
Death in the DR (per SUPP03/SUPP04)		0.2% (1/663)0% (1/663)	0.8% (5/653)1% (6/652)	0.09780.0978

Table 2. Delivery Room interventions

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Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	<0.0001*
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation	33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.0225*

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661	25.6% (167/653	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662	92.9% (606/652	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663	22.4% (146/653	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660	93.4% (609/652	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660	27.0% (176/652	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67.1% (443/660	98.9% (646/653	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=6634)	Surfactant (N=6532)	Relative Risk for CPAP vs. Surfactant (95% CI)	Unadjusted Adjusted P-value
Death in the first week	6.0%	6.0%	0.99 (0.64,	0.95750.9

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	(40/663)6% (40/664)	(39/653)6% (39/651)	1.53)	630
Death at any time while hospitalized	16.4% (109/663)16% (109/664)	19.6% (128/653)20% (127/651)	0.84 (0.67, 1.05)	0.125(90.1 440)
Total LOS any hospital (survivors only)* Mean±StdErr (N=1075)	104.8 ± 2.0(100.4 ± 42.9)	106.2 ± 2.0(101.4 ± 41.6)		0.596(70.7 047)
Days on supplemental oxygen† (survivors only)Mean±StdErr (N=1098)	62.2 ± 1.6(55.0 ± 37.8)	65.3 ± 1.6(58.5 ± 37.6)		0.121(50.1 229)
Days on mechanical vent (HFV & CV)† (survivors only)Mean±StdErr (N=1098)	24.8 ± 1.0(20.0 ± 23.9)	27.7 ± 1.1(23.2 ± 26.2)		0.028(70.0 331)
Discharge on oxygen	22.2% (122/550)22% (122/550)	23.9% (124/519)24% (124/519)	0.98 (0.8, 1.2)	0.820(20.5 067)
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)55% (362/655)	48.8% (318/652)49% (318/652)	1.14 (1.03, 1.25)	0.011(10.0 188)
Any air leak in first 14 days	7% (45/663)7% (45/663)	7% (48/653)7% (48/653)	0.89 (0.6, 1.32)	0.555(30.6 901)
Medical or surgical NEC	12.7% (83/654)13% (83/654)	9.9% (63/636)10% (63/636)	1.25 (0.92, 1.71)	0.146(90.1 144)
PDA requiring surgery	11.2% (73/653)11% (73/653)	10.7% (68/636)11% (68/636)	1 (0.73, 1.36)	0.993(70.7 793)
IVH grade 3-4	14.3% (92/642)14% (92/642)	11.5% (72/628)11% (72/628)	1.26 (0.94, 1.68)	0.122(30.1 279)
Postnatal steroids for BPD	7.2% (47/649)7% (47/650)	13.2% (83/631)13% (83/629)	0.57 (0.41, 0.78)	0.000(50.0 005)

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	~~Unadjusted~~ Adjusted P-value
Death in the first week	8.8% (25/285)~~9% (25/285)~~	10.4% (29/280)~~10% (29/280)~~	0.86 (0.51, 1.45)	0.5646~~0.52 17~~
Death at any time while hospitalized	23.9% (68/285)~~24% (68/285)~~	32.1% (90/280)~~32% (90/279)~~	0.74 (0.57, 0.98)	0.0335~~0.02 64~~*
Total LOS any hospital* ~~(survivors only)~~Mean±StdErr (N=407)	122.0 ± 2.9~~120.7 ± 47.9~~	119.0 ± 3.1~~119.2 ± 40.5~~		0.4690~~0.73 94~~
Days on supplemental oxygen† ~~(survivors only)~~Mean±StdErr (N=421)	80.8 ± 2.3~~76.9 ± 34.3~~	80.3 ± 2.4~~78.1 ± 33.5~~		0.8648~~0.72 69~~
Days on mechanical vent (HFV & CV)† ~~(survivors only)~~Mean±StdErr (N=421)	35.8 ± 1.5~~33.1 ± 27.3~~	38.7 ± 1.6~~37.5 ± 29.0~~		0.1722~~0.11 38~~
Discharge on oxygen	32.2% (69/214)~~32% (69/214)~~	31.4% (59/188)~~31% (59/188)~~	1.08 (0.82, 1.41)	0.5878~~0.85 35~~
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)~~34% (97/283)~~	26.4% (74/280)~~26% (74/280)~~	1.29 (1, 1.66)	0.0486~~0.04 29~~*
Any air leak in first 14 days	8.1% (23/285)~~8% (23/285)~~	9.6% (27/280)~~10% (27/280)~~	0.79 (0.47, 1.35)	0.3954~~0.51 05~~
Medical or surgical NEC	15.1% (42/279)~~15% (42/279)~~	13.1% (35/268)~~13% (35/268)~~	1.13 (0.74, 1.71)	0.5798~~0.50 26~~
PDA requiring surgery	16.5% (46/279)~~16% (46/279)~~	17.2% (46/268)~~17% (46/268)~~	0.9 (0.62, 1.3)	0.5819~~0.83 25~~
IVH grade 3-4	19.8% (54/273)~~20% (54/273)~~	17.0% (45/265)~~17% (45/265)~~	1.17 (0.82, 1.68)	0.3897~~0.40 22~~
Postnatal steroids for BPD	13.0% (36/276)~~13% (36/276)~~	20.5% (54/264)~~20% (54/264)~~	0.66 (0.46, 0.94)	0.0226~~0.02 09~~*

* Among survivors to discharge, transfer or one year; maximum value is 366 days
† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

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Table 2. Other outcomes for CPAP vs. Surfactant

Characteristic	Category	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week		6.0% (40/663)	6.0% (39/653)	0.99 (0.64, 1.53)	0.9575
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1079)	101.4 ± 2.0	101.5 ± 2.0		0.9444
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=1082)	57.5 ± 0.9	58.8 ± 0.9		0.2240
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	17.3 ± 0.6	16.8 ± 0.6		0.4713
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	3.4 ± 0.3	3.7 ± 0.3		0.4552
Discharge on oxygen (NG03 or NG05)		22.2% (122/550)	23.9% (124/519)	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)	0.0111
Pneumothorax (NG03 or SUPP08)		8.1% (54/663)	5.5% (36/653)	1.46 (0.96, 2.21)	0.0786
Any air leak in first 14 days (SUPP08)		6.8% (45/663)	7.4% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC (NG03)		12.7% (83/654)	9.9% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery (NG03)		11.2% (73/653)	10.7% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4 (NG03)		14.3% (92/642)	11.5% (72/628)	1.26 (0.94, 1.68)	0.1223
PVL (NG03 or MRI01)		4.4% (28/643)	4.1% (26/629)	1.09 (0.63, 1.88)	0.7538
Death or PVL (NG03 or MRI01)		20.2% (134/663)	22.5% (147/653)	0.9 (0.74, 1.11)	0.3185
Postnatal steroids for BPD (NG03)		7.2% (47/649)	13.2% (83/631)	0.57 (0.41, 0.78)	0.0005
Postnatal steroids after DOL 21 (SUPP09)		17.3% (114/659)	22.9% (149/652)	0.75 (0.61, 0.92)	0.0069
Intubated in DR (SUPP03)		34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		76.9% (508/661)	99.5% (649/652)	0.77 (0.74, 0.8)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		83.1% (551/663)	99.7% (651/653)	0.83 (0.8, 0.86)	<0.0001

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Table 2. Other outcomes for CPAP vs. Surfactant Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week		8.8% (25/285)	10.4% (29/280)	0.86 (0.51, 1.45)	0.5646
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=405)	122.0 ± 2.9	119.0 ± 3.1		0.4690
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=407)	118.0 ± 2.9	116.0 ± 3.1		0.6331
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=421)	68.7 ± 1.3	68.6 ± 1.3		0.9669
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	19.5 ± 0.9	18.0 ± 1.0		0.2355
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	4.9 ± 0.4	5.1 ± 0.4		0.8283
Discharge on oxygen (NG03 or NG05)		32.2% (69/214)	31.4% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.0486
Pneumothorax (NG03 or SUPP08)		10.2% (29/285)	7.5% (21/280)	1.29 (0.74, 2.26)	0.3626
Any air leak in first 14 days (SUPP08)		8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC (NG03)		15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery (NG03)		16.5% (46/279)	17.2% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4 (NG03)		19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.3897
PVL (NG03 or MRI01)		6.2% (17/273)	5.3% (14/265)	1.23 (0.6, 2.52)	0.5684
Death or PVL (NG03 or MRI01)		29.1% (83/285)	35.7% (100/280)	0.82 (0.65, 1.05)	0.1180
Postnatal steroids for BPD (NG03)		13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.0226
Postnatal steroids after DOL 21 (SUPP09)		27.7% (78/282)	33.7% (94/279)	0.8 (0.63, 1.02)	0.0697
Intubated in DR (SUPP03)		51.1% (145/284)	93.9% (263/280)	0.54 (0.48, 0.61)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		87.7% (250/285)	99.3% (278/280)	0.88 (0.84, 0.92)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		93.7% (267/285)	99.6% (279/280)	0.94 (0.91, 0.97)	0.0003

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Table 2. Other outcomes for CPAP vs. Surfactant Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week		4.0% (15/378)	2.7% (10/373)	1.36 (0.61, 3.02)	0.4561
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4		0.2147
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=672)	85.1 ± 2.4	86.5 ± 2.4		0.6422
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9		0.0349
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3		0.0848
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=661)	46.5 ± 1.1	48.8 ± 1.1		0.1113
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	15.3 ± 0.8	15.3 ± 0.8		0.9790
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	1.9 ± 0.3	2.3 ± 0.3		0.4346
Discharge on oxygen (NG03 or NG05)		15.8% (53/336)	19.6% (65/331)	0.88 (0.64, 1.2)	0.4118
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.1016
Pneumothorax (NG03 or SUPP08)		6.6% (25/378)	4.0% (15/373)	1.69 (0.9, 3.17)	0.1021
Any air leak in first 14 days (SUPP08)		5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.9652
Medical or surgical NEC (NG03)		10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.1353
PDA requiring surgery (NG03)		7.2% (27/374)	6.0% (22/368)	1.22 (0.7, 2.14)	0.4875
IVH grade 3-4 (NG03)		10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.1732
PVL (NG03 or MRI01)		3.0% (11/370)	3.3% (12/364)	0.92 (0.4, 2.12)	0.8434
Death or PVL (NG03 or MRI01)		13.5% (51/378)	12.6% (47/373)	1.07 (0.74, 1.55)	0.7304
Postnatal steroids for BPD (NG03)		2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.0076
Postnatal steroids after DOL 21 (SUPP09)		9.5% (36/377)	14.7% (55/373)	0.67 (0.45, 0.99)	0.0433
Intubated in DR (SUPP03)		21.8% (82/376)	93.0% (346/372)	0.24 (0.2, 0.29)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		68.6% (258/376)	99.7% (371/372)	0.68 (0.64, 0.74)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		75.1% (284/378)	99.7% (372/373)	0.75 (0.7, 0.79)	<0.0001

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Table 1 Patient Description for CPAP vs. Surfactant

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43.0% (285/663)	42.9% (280/653)	0.9686
	26-27	57.0% (378/663)	57.1% (373/653)	
Male		51.6% (342/663)	56.7% (370/653)	0.0646
Race/ethnicity	Non-Hispanic Black	38.3% (254/663)	36.0% (235/653)	0.3681
	Non-Hispanic White	37.7% (250/663)	41.5% (271/653)	
	Hispanic	20.8% (138/663)	18.5% (121/653)	
	Other/unknown	3.2% (21/663)	4.0% (26/653)	
Birth weight (grams)	Mean (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Antenatal steroids (any)		96.8% (642/663)	95.6% (623/652)	0.2248
Antenatal steroids (full course)		73.6% (486/660)	69.8% (453/649)	0.1232
Death in the DR (SUPP03/SUPP04)		0.2% (1/663)	0.8% (5/653)	0.0978

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Table 1b. DR outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23.3% (154/661)	25.6% (167/653)	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	65.7% (435/662)	92.9% (606/652)	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81.1% (538/663)	22.4% (146/653)	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660)	27.0% (176/652)	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14.1% (93/660)	51.4% (335/652)	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67.1% (443/660)	98.9% (646/653)	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5.5% (36/660)	6.1% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		51.6% (147/285)	57.9% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	42.8% (122/285)	37.9% (106/280)	0.0495*
	Non-Hispanic White	32.3% (92/285)	42.9% (120/280)	
	Hispanic	22.1% (63/285)	16.1% (45/280)	
	Other/unknown	2.8% (8/285)	3.2% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.3 ± 139.5	0.0713
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1149
Apgar at 1 minute <3		31.0% (88/284)	30.0% (84/280)	0.7993
Apgar at 5 minutes <3		6.7% (19/285)	6.8% (19/280)	0.9550
PPV in the DR (SUPP03)		72.9% (207/284)	95.4% (267/280)	<0.0001*
CPAP in the DR (SUPP03)		71.9% (205/285)	22.1% (62/280)	<0.0001*
Intubated in DR (SUPP03)		51.1% (145/284)	93.9% (263/280)	<0.0001*
DR intubation for resuscitation		48.2% (137/284)	31.1% (87/280)	<0.0001*
Surfactant in DR (SUPP03)		21.1% (60/284)	53.2% (149/280)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		77.5% (220/284)	98.6% (276/280)	<0.0001*
Chest compressions in DR (SUPP03)		9.5% (27/285)	8.2% (23/280)	0.5982
Epinephrine in DR (SUPP03)		3.5% (10/285)	5.4% (15/280)	0.2854
Antenatal steroids (any)		97.9% (279/285)	97.1% (271/279)	0.5608
Antenatal steroids (full course)		78.6% (224/285)	72.7% (202/278)	0.1009
Death in the DR (SUPP03/SUPP04)		0.4% (1/285)	1.4% (4/280)	0.1715

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Table 1: Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Male		51.6% (195/378)	55.8% (208/373)	0.2511
Race/ethnicity	Non-Hispanic Black	34.9% (132/378)	34.6% (129/373)	0.8733
	Non-Hispanic White	41.8% (158/378)	40.5% (151/373)	
	Hispanic	19.8% (75/378)	20.4% (76/373)	
	Other/unknown	3.4% (13/378)	4.6% (17/373)	
Birth weight (grams)	Mean (n=751)	922.2 ± 180.5	921.0 ± 181.4	0.9325
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.9676
Apgar at 1 minute <3		17.5% (66/377)	22.3% (83/373)	0.1034
Apgar at 5 minutes <3		1.9% (7/378)	3.5% (13/373)	0.1645
PPV in the DR (SUPP03)		60.3% (228/378)	91.1% (339/372)	<0.0001*
CPAP in the DR (SUPP03)		88.1% (333/378)	22.5% (84/373)	<0.0001*
Intubated in DR (SUPP03)		21.8% (82/376)	93.0% (346/372)	<0.0001*
DR intubation for resuscitation		20.7% (78/376)	23.9% (89/372)	0.2964
Surfactant in DR (SUPP03)		8.8% (33/376)	50.0% (186/372)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		59.3% (223/376)	99.2% (370/373)	<0.0001*
Chest compressions in DR (SUPP03)		2.4% (9/375)	4.6% (17/373)	0.1072
Epinephrine in DR (SUPP03)		0.8% (3/375)	3.2% (12/373)	0.0184*
Antenatal steroids (any)		96.0% (363/378)	94.4% (352/373)	0.2865
Antenatal steroids (full course)		69.9% (262/375)	67.7% (251/371)	0.5146
Death in the DR (SUPP03/SUPP04)		0.0% (0/378)	0.3% (1/373)	0.3138

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Table 3: BPD outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	16.4% (109/663)	19.6% (128/653)	0.84 (0.67, 1.05)	0.1259
Death by 36 weeks PMA	14.2% (94/663)	17.5% (114/653)	0.81 (0.63, 1.03)	0.0890
BPD (physiologic definition)	39.2% (223/569)	40.6% (219/539)	0.99 (0.87, 1.14)	0.9172
BPD (physiologic definition) or death by 36 weeks PMA	47.8% (317/663)	51.0% (333/653)	0.95 (0.85, 1.05)	0.3039
BPD (supplemental O2)	40.2% (229/569)	44.3% (239/539)	0.94 (0.82, 1.06)	0.3178
BPD (supplemental O2) or death by 36 weeks PMA	48.7% (323/663)	54.1% (353/653)	0.91 (0.83, 1.01)	0.0719
ROP	13.5% (70/517)	14.2% (68/480)	0.95 (0.7, 1.28)	0.7406
ROP or death	28.4% (176/620)	32.1% (193/601)	0.87 (0.74, 1.03)	0.0971

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3. BPD outcomes for CPAP vs. Surfactant Where GA is 24-25 weeks

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	23.9% (68/285)	32.1% (90/280)	0.74 (0.57, 0.98)	0.0335
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.0125
BPD (physiologic definition)	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.4570
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.4470
BPD (supplemental O2)	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.5329
BPD (supplemental O2) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.3578
ROP	23.3% (47/202)	31.4% (55/175)	0.75 (0.54, 1.05)	0.0994
ROP or death	42.1% (112/266)	55.2% (144/261)	0.74 (0.62, 0.89)	0.0015

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3: BPD outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	10.8% (41/378)	10.2% (38/373)	1.06 (0.7, 1.6)	0.7966
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.6055
BPD (physiologic definition)	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.4621
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.4828
BPD (supplemental O2)	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.0812
BPD (supplemental O2) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.1163
ROP	7.3% (23/315)	4.3% (13/305)	1.86 (0.94, 3.67)	0.0728
ROP or death	18.1% (64/354)	14.4% (49/340)	1.25 (0.88, 1.77)	0.2153

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 2:47:34 PM

Rose
I would go with the following:
Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
Ed and Vivek on the CPAP/surfactant
Kurt and Vivek on the saturation paper.
Tx, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 2:17 PM
To: Laptook, Abbot
Subject: RE: Saturation paper

Yes, site PI

Ed was originally on the subcommittee and with re-competition, Kurt took over

Rose

From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Monday, November 09, 2009 2:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

What was Vivek's role; site PI?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 12:27 PM
To: 'Finer, Neil'; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; Roger Faix; Brad Yoder (Bradley.yoder@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; mcw3@case.edu; Laptook, Abbot; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

Kurt has proposed an alternative for the CPAP/surf paper. As many of you are likely to recall, Ed Donovan organized the SUPPORT training and the video in 2004. Let me know if ED and Vivek can appear on the CPAP/surf paper.

Thanks
Rose

From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, November 09, 2009 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper

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Importance: High

Hi Rose,
Personally, I would like to advocate that Ed Donovan and Vivek Narendran both be listed as Cincinnati authors on the CPAP Surfactant manuscript since Ed and Vivek did a lot to move forward the study up front and Vivek was instrumental during the trial. (Ed did a lot with initial start up and education, hosting the training, producing the training video, and was the Cincinnati PI at the beginning of the study). I would like to be listed as the author from Cincinnati on the Oxygen Saturation.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736-(b) (6)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
___X__ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
_____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

_____ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,

Just wondering,

Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.

Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS O2 saturation abstract for NIH clearance
Date: Monday, November 09, 2009 2:47:27 PM

I don't think so. Can you do it? THANKS.

Wally Carlo, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 1:44 PM
To: Wally Carlo, M.D.
Subject: RE: PAS O2 saturation abstract for NIH clearance

OK
Did Dr. Randolph send his out to FU and GDB?? Let me know – I can send it out and tell folks to comment by tonight.

Thanks
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 2:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS O2 saturation abstract for NIH clearance

Rose:

I will correct the two typos, and as soon as I hear about changing "death before discharge" to "death" in the table, I will send you a revised abstract.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 1:25 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance

I corrected a couple of typos in the abstract (attached). Also, I wonder if it will be confusing to refer to "oxygen use" in the text but BPD in the table? Finally, we are referring to "death before discharge" in the abstracts and manuscripts, but two of the deaths are cases that were actually "discharged home to die" per the center. It's a small distinction that might not merit any rephrasing of the outcome, but I just wanted to point it out. The two deaths are recorded on the NG03.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 2:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: PAS O2 saturation abstract for NIH clearance

Hi Rose and all:

Enclosed is the O2 sat abstract. My title is more specific than Neil's. See which style you all prefer. I am concerned using Neil's because then both would have the same title.

I had to shorten the table as no more data would fit in.

Wally

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From: Gantz, Marie
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: RE: PAS O2 saturation abstract for NIH clearance
Date: Monday, November 09, 2009 2:24:47 PM
Attachments: randomized o2 MG.docx

I corrected a couple of typos in the abstract (attached). Also, I wonder if it will be confusing to refer to "oxygen use" in the text but BPD in the table? Finally, we are referring to "death before discharge" in the abstracts and manuscripts, but two of the deaths are cases that were actually "discharged home to die" per the center. It's a small distinction that might not merit any rephrasing of the outcome, but I just wanted to point it out. The two deaths are recorded on the NG03.

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828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 2:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: PAS O2 saturation abstract for NIH clearance

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First Author: W A Carlo **File Number:** 751587

Presenting Author: W A Carlo

Responsible Author: W A Carlo

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Waldemar A Carlo MD

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Responsible Author: W A Carlo, MD

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Responsible Author Declaration:
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Presenting Author: W A Carlo, MD

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Phone: 1-205-934-4680 **Fax:** 1-205-934-3100

Presenter E-mail: wcarlo@peds.uab.edu

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Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

Awards Applied for:

Consider for PAS Travel Grant Award: No

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Is the Sponsor an Author? Yes
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Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants-the SUPPORT Trial

W A Carlo, MD[1], N N Finer, MD[2] and on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. [1]University of Alabama at Birmingham, Birmingham, Alabama, United States and [2]University of California San Diego, San Diego, California, United States.

Background: Recent non-randomized studies suggest that the incidence of retinopathy of prematurity (ROP) decreases in premature infants with oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce ROP without increasing adverse outcomes

Objective: To test the hypothesis that a lower oxygen saturation target decreases severe ROP and/or death in extremely premature infants.

Design/Methods: 1316 infants of 24 0/7 to 27 6/7 weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters ~~or~~ as part of a 2x2 factorial trial. The primary outcome was a composite of severe ROP (Type 1 threshold ROP/surgery/bevacizumab) and/or death.

Results: Severe ROP/death did not differ between the oxygen saturation target groups (Table; adjusted for stratification factors: study center, gestational age group, and familial clustering). Severe ROP was decreased (P<0.001) in the lower oxygen saturation target group but death was more frequent (P=0.0415, Table). Oxygen use at 36 weeks significantly decreased in the lower oxygen saturation target group but oxygen use by the physiologic definition or oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups (Table).

Conclusions: Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of severe ROP/death but resulted in an increase in mortality that partially offset a decrease in severe ROP. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term ROP benefits.

	Lower O2 Saturation Group n/N (%)	Higher O2 Saturation Group n/N (%)	Adjusted Relative Risk1 (95% CI)
Severe ROP/death	170/605 (28.3)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe ROP	43/483 (8.9)	95/514 (18.5)	0.51 (0.37, 0.71)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia (physiologic) at 36 weeks	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: PAS O2 saturation abstract for NIH clearance
Date: Monday, November 09, 2009 2:00:26 PM
Attachments: randomized o2.docx

Hi Rose and all:

Enclosed is the O2 sat abstract. My title is more specific than Neil's. See which style you all prefer. I am concerned using Neil's because then both would have the same title.

I had to shorten the table as no more data would fit in.

Wally

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First Author: W A Carlo **File Number:** 751587

Presenting Author: W A Carlo

Responsible Author: W A Carlo

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Waldemar A Carlo MD

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Phone: 1-205-934-4680 **Fax:** 1-205-934-3100 **E-mail:** wcarlo@peds.uab.edu

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Responsible Author: W A Carlo, MD

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Responsible Author E-mail: wcarlo@peds.uab.edu

Responsible Author Declaration:
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Presenting Author: W A Carlo, MD

Department/Institution/Address: Division of Neonatology, University of Alabama at Birmingham, 619 19TH ST S, NHB 525, Birmingham, Alabama, 35249, United States

Phone: 1-205-934-4680 **Fax:** 1-205-934-3100

Presenter E-mail: wcarlo@peds.uab.edu

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Is Presenting Author a Trainee? No, Not a Trainee

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Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

Awards Applied for:

Consider for PAS Travel Grant Award: No

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Sponsored by: Waldemar A Carlo,
Email: wcarlo@peds.uab.edu
Is the Sponsor an Author? Yes

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American Pediatric Society
Society for Pediatric Research
American Academy of Pediatrics

Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants-the SUPPORT Trial

W A Carlo, MD[1], N N Finer, MD[2] and on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. [1]University of Alabama at Birmingham, Birmingham, Alabama, United States and [2]University of California San Diego, San Diego, California, United States.

Background: Recent non-randomized studies suggest that the incidence of retinopathy of prematurity (ROP) decreases in premature infants with oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce ROP without increasing adverse outcomes

Objective: To test the hypothesis that a lower oxygen saturation target decreases severe ROP and/or death in extremely premature infants.

Design/Methods: 1316 infants of 24 0/7 to 27 6/7 weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters or part of a 2x2 factorial trial. The primary outcome was a composite of severe ROP (Type 1 threshold ROP/surgery/bevacizumab) and/or death.

Results: Severe ROP/death did not differ between the oxygen saturation target groups (Table; adjusted for stratification factors: study center, gestational age group, and familial clustering). Severe ROP was decreased (P<0.001) in the lower oxygen saturation target group but death was more frequent (P=0.045, Table). Oxygen use at 36 weeks significantly decreased in the lower oxygen saturation target group but oxygen use by the physiologic definition or oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups (Table).

Conclusions: Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of severe ROP/death but resulted in an increase in mortality that partially offset a decrease in severe ROP. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term ROP benefits.

	Lower O2 Saturation Group n/N (%)	Higher O2 Saturation Group n/N (%)	Adjusted Relative Risk1 (95% CI)
Severe ROP/death	170/605 (28.3)	198/616 (32.1)	0.90 (0.76, 1.06)
Severe ROP	43/483 (8.9)	95/514 (18.5)	0.51 (0.37, 0.71)
Death before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia (physiologic) at 36 weeks	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)

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From: Gantz, Marie
To: Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 1:50:13 PM
Attachments: T3S Other Outcomes - 09NOV09.doc.rtf
T1S Baseline Characteristics - 09NOV09.doc.rtf
T2S Major Outcomes - 09NOV09.doc
Oxygen Saturation Target.11.6.09.MASTER_MG2.doc

Wally,

Here are the paper and source tables in which percentages now have a decimal.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 12:23 PM
To: Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Ok, done

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
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-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 09, 2009 10:48 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I agree with Marie that we should call it severe ROP or death, and then define severe ROP as threshold ROP or ROP requiring surgery.

Thanks

Abhik

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-----Original Message-----
From: Gantz, Marie
Sent: Monday, November 09, 2009 11:45 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.

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Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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SpO2 Paper Table 3. Other Outcomes for Low vs. High SpO2

Characteristic	Category	Low SpO2 (N=654)	High SpO2 (N=662)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1075)	104.5 ± 2.0	106.4 ± 2.0		0.4477
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1079)	99.8 ± 2.0	103.0 ± 2.0		0.2175
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	25.5 ± 1.1	26.9 ± 1.0		0.3021
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	59.8 ± 1.6	67.4 ± 1.5		0.0002
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	17.1 ± 0.6	17.0 ± 0.6		0.9391
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	3.3 ± 0.3	3.8 ± 0.3		0.1362
Alive and off MV (HFV/CV) at 14 days (NG07 or SUPP05)		332/644 (51.6)	326/655 (49.8)	1.01 (0.91, 1.12)	0.8564
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		351/648 (54.2)	329/659 (49.9)	1.06 (0.96, 1.16)	0.2695

NOTE: Length of stay is up to one year (NG05 status)
NOTE: Duration of vent/O2/CPAP/nSIMV is up to 120 days (NG03 status)

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SpO2 Paper Table 1. Baseline Characteristics for High vs. Low SpO2

Characteristic	Category	Low SpO2 (N=654)	High SpO2 (N=662)	Unadjusted P-value
Birth weight (grams)	Mean±StdDev (n=1316)	835.5 ± 193.4	824.8 ± 193.0	0.3138
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.1 ± 1.1	0.3925
Multiple birth (per NG02)		161/654 (24.6)	176/662 (26.6)	0.4134
Higher order multiple birth (3 or 4)		30/654 (4.6)	31/662 (4.7)	0.9343
Male		341/654 (52.1)	371/662 (56.0)	0.1556
Race/ethnicity	Non-Hispanic Black	257/654 (39.3)	232/662 (35.0)	0.2642
	Non-Hispanic White	242/654 (37.0)	279/662 (42.1)	
	Hispanic	132/654 (20.2)	127/662 (19.2)	
	Other/unknown	23/654 (3.5)	24/662 (3.6)	
Antenatal steroids (any)		633/654 (96.8)	632/661 (95.6)	0.2648
Antenatal steroids (full course)		477/651 (73.3)	462/658 (70.2)	0.2191
Apgar at 5 minutes <3		34/654 (5.2)	24/662 (3.6)	0.1644
Surfactant in DR or NICU (SUPP03, SUPP04)		531/653 (81.3)	558/660 (84.5)	0.1200

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SpO2 Paper Table 1: Baseline Characteristics for High vs. Low SpO2 Where GA is 24-25 weeks

Characteristic	Category	Low SpO2 (N=276)	High SpO2 (N=289)	Unadjusted P-value
Birth weight (grams)	Mean±StdDev (n=565)	705.3 ± 131.4	711.5 ± 133.7	0.5838
Gestational age at birth (weeks)	Mean±StdDev (n=565)	25.1 ± 0.6	25.1 ± 0.5	0.5518
Multiple birth (per NG02)		55/276 (19.9)	75/289 (26.0)	0.0890
Higher order multiple birth (3 or 4)		3/276 (1.1)	17/289 (5.9)	0.002*
Male		139/276 (50.4)	170/289 (58.8)	0.0434*
Race/ethnicity	Non-Hispanic Black	121/276 (43.8)	107/289 (37.0)	0.0974
	Non-Hispanic White	94/276 (34.1)	118/289 (40.8)	
	Hispanic	56/276 (20.3)	52/289 (18.0)	
	Other/unknown	5/276 (1.8)	12/289 (4.2)	
Antenatal steroids (any)		271/276 (98.2)	279/288 (96.9)	0.3163
Antenatal steroids (full course)		213/276 (77.2)	213/287 (74.2)	0.4136
Apgar at 5 minutes <3		22/276 (8.0)	16/289 (5.5)	0.2481
Surfactant in DR or NICU (SUPP03, SUPP04)		235/276 (85.1)	261/288 (90.6)	0.0457*

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SpO2 Paper Table 1 Baseline Chatacteristics for High vs. Low SpO2
Where GA is 26-27 weeks

Characteristic	Category	Low SpO2 (N=378)	High SpO2 (N=373)	Unadjusted p-value*
Birth weight (grams)	Mean±StdDev (n=751)	930.5 ± 175.2	912.6 ± 186.1	0.1733
Gestational age at birth (weeks)	Mean±StdDev (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.6046
Multiple birth (per NG02)		106/378 (28.0)	101/373 (27.1)	0.7674
Higher order multiple birth (3 or 4)		27/378 (7.1)	14/373 (3.8)	0.0409*
Male		202/378 (53.4)	201/373 (53.9)	0.9020
Race/ethnicity	Non-Hispanic Black	136/378 (36.0)	125/373 (33.5)	0.5351
	Non-Hispanic White	148/378 (39.2)	161/373 (43.2)	
	Hispanic	76/378 (20.1)	75/373 (20.1)	
	Other/unknown	18/378 (4.8)	12/373 (3.2)	
Antenatal steroids (any)		362/378 (95.8)	353/373 (94.6)	0.4689
Antenatal steroids (full course)		264/375 (70.4)	249/371 (67.1)	0.3332
Apgar at 5 minutes <3		12/378 (3.2)	8/373 (2.1)	0.3808
Surfactant in DR or NICU (SUPP03, SUPP04)		296/377 (78.5)	297/372 (79.8)	0.6555

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SpO2 Paper Table 2. Other Outcomes for Low vs. High SpO2

Characteristic	Low SpO2 (N=654)	High SpO2 (N=662)	Relative RISK for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	171/605 (28.3)	198/616 (32.1)	0.9 (0.76, 1.06)	0.2050
ROP	43/483 (8.9)	95/514 (18.5)	0.51 (0.37, 0.71)	0.0001
Death at any time while hospitalized	130/654 (19.9)	107/662 (16.2)	1.27 (1.01, 1.6)	0.0412
Death in the first week	41/654 (6.3)	38/662 (5.7)	1.11 (0.72, 1.72)	0.6430
Death in the first 14 days	64/654 (9.8)	56/662 (8.5)	1.2 (0.84, 1.7)	0.3140
Death by 36 weeks PMA	114/654 (17.4)	94/662 (14.2)	1.27 (0.99, 1.63)	0.0610
BPD (supplemental O2)	203/540 (37.6)	265/568 (46.7)	0.82 (0.72, 0.93)	0.0020
BPD (supplemental O2) or death by 36 weeks PMA	317/654 (48.5)	359/662 (54.2)	0.91 (0.83, 1.01)	0.0754
BPD (physiologic definition)	205/540 (38.0)	237/568 (41.7)	0.92 (0.81, 1.05)	0.2339
BPD (physiologic definition) or death by 36 weeks PMA	319/654 (48.8)	331/662 (50.0)	0.99 (0.9, 1.1)	0.8988
IVH grade 3-4 (NG03)	83/630 (13.2)	81/640 (12.7)	1.06 (0.8, 1.4)	0.6997
Death or IVH grade 3-4 (NG03)	179/653 (27.4)	156/661 (23.6)	1.18 (0.99, 1.42)	0.0663
PVL (NG03 or MRI01)	24/631 (3.8)	30/641 (4.7)	0.83 (0.49, 1.42)	0.4996
Death or PVL (NG03 or MRI01)	149/654 (22.8)	132/662 (19.9)	1.18 (0.96, 1.45)	0.1102
Medical or surgical NEC (NG03)	76/641 (11.9)	70/649 (10.8)	1.11 (0.82, 1.51)	0.5076
Death or medical/surgical NEC (NG03)	176/654 (26.9)	155/662 (23.4)	1.18 (0.98, 1.43)	0.0746
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	228/624 (36.5)	226/634 (35.6)	1.03 (0.89, 1.18)	0.7104
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	300/654 (45.9)	291/662 (44.0)	1.05 (0.94, 1.18)	0.3876
PDA (any) (NG03)	307/641 (47.9)	324/648 (50.0)	0.96 (0.86, 1.07)	0.4320
PDA medical treatment (NG03)	219/634 (34.5)	233/645 (36.1)	0.95 (0.82, 1.09)	0.4689
PDA requiring surgery (NG03)	73/641 (11.4)	68/648 (10.5)	1.09 (0.8, 1.48)	0.5758
Pneumothorax (NG03 or SUPP08)	47/654 (7.2)	43/662 (6.5)	1.12 (0.74, 1.68)	0.6036
Any air leak in first 14 days (SUPP08)	51/654 (7.8)	42/662 (6.3)	1.23 (0.83, 1.83)	0.2941
Postnatal steroids for BPD (NG03)	61/636 (9.6)	69/644 (10.7)	0.91 (0.67, 1.24)	0.5449
Postnatal steroids after DOL 21 (SUPP09)	123/650 (18.9)	140/661 (21.2)	0.91 (0.74, 1.12)	0.3850

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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SpO2 Paper Table 2. Other Outcomes for High vs. Low SpO2
Where GA is 24-25 weeks

Characteristic	Low SpO2 (N=276)	High SpO2 (N=289)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	117/256 (45.7)	139/271 (51.3)	0.88 (0.73, 1.05)	0.1648
ROP	34/176 (19.3)	68/201 (33.8)	0.58 (0.4, 0.84)	0.0039
Death at any time while hospitalized	85/276 (30.8)	73/289 (25.3)	1.24 (0.94, 1.64)	0.1225
Death in the first week	26/276 (9.4)	28/289 (9.7)	0.96 (0.57, 1.64)	0.8905
Death in the first 14 days	41/276 (14.9)	40/289 (13.8)	1.12 (0.73, 1.71)	0.6073
Death by 36 weeks PMA	75/276 (27.2)	64/289 (22.1)	1.26 (0.93, 1.71)	0.1370
BPD (supplemental O2)	101/201 (50.2)	127/225 (56.4)	0.89 (0.75, 1.04)	0.1471
BPD (supplemental O2) or death by 36 weeks PMA	176/276 (63.8)	191/289 (66.1)	0.97 (0.86, 1.1)	0.6547
BPD (physiologic definition)	105/201 (52.2)	128/225 (56.9)	0.91 (0.78, 1.07)	0.2645
BPD (physiologic definition) or death by 36 weeks PMA	180/276 (65.2)	192/289 (66.4)	0.99 (0.88, 1.11)	0.8024
IVH grade 3-4 (NG03)	47/263 (17.9)	52/275 (18.9)	0.98 (0.69, 1.4)	0.9012
Death or IVH grade 3-4 (NG03)	108/276 (39.1)	101/289 (34.9)	1.14 (0.92, 1.41)	0.2474
PVL (NG03 or MRI01)	13/263 (4.9)	18/275 (6.5)	0.78 (0.39, 1.58)	0.4956
Death or PVL (NG03 or MRI01)	95/276 (34.4)	88/289 (30.4)	1.16 (0.9, 1.48)	0.2467
Medical or surgical NEC (NG03)	39/269 (14.5)	38/278 (13.7)	1.05 (0.69, 1.59)	0.8369
Death or medical/surgical NEC (NG03)	104/276 (37.7)	98/289 (33.9)	1.13 (0.9, 1.42)	0.3079
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	124/258 (48.1)	133/269 (49.4)	0.97 (0.82, 1.15)	0.7232
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	168/276 (60.9)	174/289 (60.2)	1.01 (0.89, 1.16)	0.8466
PDA (any) (NG03)	146/269 (54.3)	154/278 (55.4)	0.99 (0.85, 1.14)	0.8827
PDA medical treatment (NG03)	106/265 (40.0)	110/276 (39.9)	1 (0.82, 1.21)	0.9683
PDA requiring surgery (NG03)	48/269 (17.8)	44/278 (15.8)	1.12 (0.78, 1.62)	0.5465
Pneumothorax (NG03 or SUPP08)	29/276 (10.5)	21/289 (7.3)	1.52 (0.86, 2.67)	0.1502
Any air leak in first 14 days (SUPP08)	31/276 (11.2)	19/289 (6.6)	1.69 (0.97, 2.93)	0.0633
Postnatal steroids for BPD (NG03)	46/266 (17.3)	44/274 (16.1)	1.06 (0.74, 1.52)	0.7503
Postnatal steroids after DOL 21 (SUPP09)	86/273 (31.5)	86/288 (29.9)	1.06 (0.83, 1.34)	0.6558

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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SpO2 Paper Table 2, Other Outcomes for High vs. Low SpO2
Where GA is 26-27 weeks

Characteristic	Low SpO2 (N=378)	High SpO2 (N=373)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	54/349 (15.5)	59/345 (17.1)	0.95 (0.67, 1.34)	0.7575
ROP	9/307 (2.9)	27/313 (8.6)	0.35 (0.17, 0.73)	0.0049
Death at any time while hospitalized	45/378 (11.9)	34/373 (9.1)	1.33 (0.88, 2.01)	0.1811
Death in the first week	15/378 (4.0)	10/373 (2.7)	1.51 (0.69, 3.33)	0.3017
Death in the first 14 days	23/378 (6.1)	16/373 (4.3)	1.38 (0.74, 2.55)	0.3091
Death by 36 weeks PMA	39/378 (10.3)	30/373 (8.0)	1.3 (0.83, 2.02)	0.2537
BPD (supplemental O2)	102/339 (30.1)	138/343 (40.2)	0.75 (0.62, 0.92)	0.0057
BPD (supplemental O2) or death by 36 weeks PMA	141/378 (37.3)	168/373 (45.0)	0.85 (0.71, 1)	0.0522
BPD (physiologic definition)	100/339 (29.5)	109/343 (31.8)	0.93 (0.75, 1.16)	0.5314
BPD (physiologic definition) or death by 36 weeks PMA	139/378 (36.8)	139/373 (37.3)	1 (0.83, 1.21)	0.9653
IVH grade 3-4 (NG03)	36/367 (9.8)	29/365 (7.9)	1.19 (0.74, 1.92)	0.4684
Death or IVH grade 3-4 (NG03)	71/377 (18.8)	55/372 (14.8)	1.27 (0.92, 1.75)	0.1443
PVL (NG03 or MRI01)	11/368 (3.0)	12/366 (3.3)	0.9 (0.4, 2.07)	0.8126
Death or PVL (NG03 or MRI01)	54/378 (14.3)	44/373 (11.8)	1.23 (0.85, 1.79)	0.2698
Medical or surgical NEC (NG03)	37/372 (9.9)	32/371 (8.6)	1.19 (0.75, 1.87)	0.4607
Death or medical/surgical NEC (NG03)	72/378 (19.0)	57/373 (15.3)	1.28 (0.93, 1.76)	0.1247
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	104/366 (28.4)	93/365 (25.5)	1.11 (0.88, 1.4)	0.3978
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	132/378 (34.9)	117/373 (31.4)	1.11 (0.91, 1.35)	0.3202
PDA (any) (NG03)	161/372 (43.3)	170/370 (45.9)	0.93 (0.79, 1.09)	0.3644
PDA medical treatment (NG03)	113/369 (30.6)	123/369 (33.3)	0.91 (0.74, 1.11)	0.3463
PDA requiring surgery (NG03)	25/372 (6.7)	24/370 (6.5)	1.04 (0.6, 1.81)	0.8946
Pneumothorax (NG03 or SUPP08)	18/378 (4.8)	22/373 (5.9)	0.76 (0.41, 1.4)	0.3743
Any air leak in first 14 days (SUPP08)	20/378 (5.3)	23/373 (6.2)	0.87 (0.49, 1.55)	0.6303
Postnatal steroids for BPD (NG03)	15/370 (4.1)	25/370 (6.8)	0.64 (0.34, 1.19)	0.1567
Postnatal steroids after DOL 21 (SUPP09)	37/377 (9.8)	54/373 (14.5)	0.69 (0.47, 1.02)	0.0654

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; adjusted p-value = ~~).~~ 0.205). Death was more frequent in the lower oxygen saturation target group (19.9~~20~~ vs 16.2%; RR 1.27; CI 1.01, 1.60; adjusted p-value = 0.~~)~~.041) while threshold retinopathy occurred less often in these infants (8.9 vs 18.5%; RR 0.51; CI 0.37, 0.71; adjusted p-value= ~~).~~0.0001).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

Comment [MG1]: 3 of the randomized infants were actually 28 0/7 weeks GA

Comment [MG2]: Do we need to be specific and say threshold or ROP surgery? Not all infants who had surgery for ROP also had an exam with threshold in our data.

Comment [MG3]: These numbers include 13 infants who died (6 who had ROP and 7 who did not). Do you want me to remove them so it's strictly ROP among survivors?

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than ~~85~~84% or higher than ~~95~~96%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

Comment [MG4]: The offset was 3% in the target ranges, but at points above and below the target ranges where the display values were transitioning back to "actual" values the offset was not necessarily 3%

Comment [MG5]: A display value of 84 in the high target group corresponds to actual values of 84-87. Below 84 the display values correspond to actual values in both treatment groups.

Comment [MG6]: A display value of 96 in the low target group corresponds to actual values of 93-96. Above 96 the display values correspond to actual values in both treatment groups.

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy or surgery or Avastin treatment for ROP. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present ~~up to 55 weeks post-menstrual age~~:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of categorical outcomes for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks (RR) comparing incidence rates for infants in each treatment arm who developed the

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primary outcome. Continuous outcomes were analyzed using mixed effects linear models. Survival analysis using Cox regression produced a hazard ratio (HR) for comparing mortality in the low and high oxygen saturation groups. ~~The model produces relative risk estimates~~ GEE, mixed effect and survival models were adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided adjusted p-value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and

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Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ~~——~~247 infants to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included **death, pneumothorax, intraventricular hemorrhage,** and a combination of any of the above events.

Comment [MG7]: Also need for chest compressions and/or epinephrine in the DR, pulmonary hemorrhage, and nasal breakdown requiring the discontinuation of nasal prongs.

RESULTS

1316 infants were enrolled between ~~January~~ February ~~2004~~ 2005 and ~~March~~ February 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR 0.90; CI 0.76, 1.06; ~~p=~~adjusted p-value

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0.~~-~~.205; Table 2). Death before discharge occurred in 130 of the 654 (19.9~~20~~%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16.2%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.041). Comparable results were observed for both gestational age strata. ~~Kaplan Meier Analysis indicated~~ Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (HR 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). **Threshold retinopathy** or surgical intervention for ROP **was decreased in the lower oxygen saturation targeted group** (8.9 vs 18.5%; **RR 0.51; CI 0.37, 0.71; p=0.**~~-~~).~~-~~.0001). Oxygen use at 36 weeks PMA was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks PMA and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks PMA did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

Comment [MG8]: These numbers include 13 infants who died (6 who had ROP and 7 who did not). Do you want me to remove them so it's strictly ROP among survivors?

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

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The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy or the need for surgical intervention for ROP, it also increased the risk for mortality.

This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.87% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for

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saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy or surgical intervention/death but it increased mortality and decreased threshold retinopathy or surgical intervention. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85

Comment [MG9]: Is this still true after some trials have switched to the new oximeter algorithm?

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to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 6545)	Higher Saturation Group (N = 6624)
Birthweight – g (m±SD)	835.5 ± 193.4~~835±193~~	824.8 ± 193.0~~825±193~~
Gestational age – wk (m±SD)	26.2 ± 1.1~~26±1~~	26.1 ± 1.1~~26±1~~
Male sex – no. (%)	341/654 (52.1)~~342/655 (52)~~	371/662 (56.0)~~370/661 (56)~~
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37.0)~~242/655 (37)~~	279/662 (42.1)~~279/661 (42)~~
Black (non-Hispanic)	257/654 (39.3)~~258/655 (39)~~	232/662 (35.0)~~231/661 (35)~~
Hispanic	132/654 (20.2)~~132/655 (20)~~	127/662 (19.2)~~127/661 (19)~~
Other/unknown	23/654 (3.5)~~23/655 (4)~~	24/662 (3.6)~~24/661 (4)~~
Antenatal corticosteriods (any) – no. (%)	633/654 (96.8)~~634/655 (97)~~	632/661 (95.6)~~631/660 (96)~~
Antenatal corticosteroids (full course) – no. (%)	477/651 (73.3)~~478/652 (73)~~	462/658 (70.2)~~460/657 (70)~~
5-min Apgar score < 3 – no. (%)	34/654 (5.2)~~34/655 (5)~~	24/662 (3.6)~~24/661 (4)~~
Surfactant in the DR or NICU – no. (%)	531/653 (81.3)~~532/654 (81)~~	558/660 (84.5)~~557/659 (85)~~

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Table 2. Major Outcomes

~~Predischarge o~~Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy or surgical intervention/death	171/605 (28.3)~~170/605 (28)~~	198/616 (32.1)~~198/616 (32)~~	0.90 (0.76, 1.06)
Threshold retinopathy or surgical intervention	43/483 (8.9)~~43/483 (9)~~	95/514 (18.5)~~95/514 (18)~~	0.51 (0.37, 0.71)
Death before discharge	130/654 (19.9)~~130/654 (20)~~	107/662 (16.2)~~107/662 (16)~~	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6.3)~~41/654 (6)~~	38/662 (5.7)~~38/661 (6)~~	1.11 (0.72, 1.72)
Death by 14 days	64/654 (9.8)~~64/654 (10)~~	56/662 (8.5)~~56/661 (8)~~	1.20 ~~(1.2~~ (0.84, 1.70)
Death by 36 weeks PMA	114/654 (17.4)~~114/654 (17)~~	94/662 (14.2)~~94/662 (14)~~	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/540 (37.6)~~202/540 (37)~~	265/568 (46.7)~~265/568 (47)~~	0.82~~1~~ (0.72~~1~~, 0.93~~2~~)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317/654 (48.5)~~316/654~~	359/662 (54.2)~~359/662~~	0.91 (0.83~~2~~, 1.01)

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	~~(48)~~	~~(54)~~		
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38.0)~~205/540~~ ~~(38)~~	237/568 (41.7)~~237/568~~ ~~(42)~~	0.92 (0.81, 1.05)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (48.8)~~319/654~~ ~~(49)~~	331/662 (50.0)~~331/662~~ ~~(50)~~	0.99 (0.90, 1.10)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)~~83/630~~ ~~(13)~~	81/640 (12.7)~~81/640~~ ~~(13)~~	1.06 (0.80, 1.40)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27.4)~~179/653~~ ~~(27)~~	156/661 (23.6)~~156/661~~ ~~(24)~~	1.18 (0.99, 1.42)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Periventricular leukomalacia	24/631 (3.8)~~24/631 (4)~~	30/641 (4.7)~~30/641 (5)~~	0.83 (0.49, 1.42)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Periventricular leukomalacia or death	149/654 (22.8)~~149/654~~ ~~(23)~~	132/662 (19.9)~~132/662~~ ~~(20)~~	1.18 (0.96, 1.45)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Necrotizing enterocolitis, stage ≥ 2	76/641 (11.9)~~76/641~~ ~~(12)~~	70/649 (10.8)~~70/649~~ ~~(11)~~	1.11 (0.82, 1.51)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (26.9)~~176/654~~ ~~(27)~~	155/662 (23.4)~~155/662~~ ~~(23)~~	1.18 (0.98, 1.43)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Late onset sepsis	228/624 (36.5)~~228/624~~ ~~(37)~~	226/634 (35.6)~~226/634~~ ~~(36)~~	1.03 (0.89, 1.18)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt
Late onset sepsis or death	300/654	291/662	1.05 (0.94, 1.18)	**Formatted:** Font: (Default) Times New Roman, 10 pt **Formatted:** Font: (Default) Times New Roman, 10 pt

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	(45.9)~~300/654~~	(44.0)~~291/662~~		
	(~~46~~)	(~~44~~)		
Patent ductus arteriosus	307/641	324/648	0.96 (0.86, 1.07)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(47.9)~~307/641~~	(50.0)~~324/648~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
	(~~48~~)	(~~50~~)		
Medical treatment for patent ductus arteriosus	219/634	233/645	0.95 (0.82, 1.09)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(34.5)~~219/634~~	(36.1)~~233/645~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
	(~~36~~)	(~~36~~)		
Surgical treatment for patent ductus arteriosus	73/641	68/648	1.09 (0.80, 1.48)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(11.4)~~73/641~~	(10.5)~~68/648~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
	(~~11~~)	(~~11~~)		
Pneumothorax – no. (%)	47/654	43/662	1.12 (0.74, 1.68)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(7.2)~~47/654 (7)~~	(6.5)~~42/662 (6)~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
Any air ~~leaks~~ leaks in the first 14 days – no. (%)	51/654	42/662	1.23 (0.83, 1.83)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(7.8)~~51/654 (8)~~	(6.3)~~42/662 (6)~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
Postnatal steroids for bronchopulmonary dysplasia	61/636	69/644	0.91 (0.67, 1.24)	**Formatted:** Font: (Default) Times New Roman, 10 pt
	(9.6)~~61/636 (10)~~	(10.7)~~69/644~~		**Formatted:** Font: (Default) Times New Roman, 10 pt
		(~~11~~)		

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

~~Characteristic~~Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P-value[1]
Length of stay any hospital, (days) m+~~SD~~SE*	104.5 ± 2.0~~99±39~~	106.4 ± 2.0~~102±43~~	0.45~~0.17~~
Length of stay NRN hospital, (days) m+~~SD~~SE*	99.8 ± 2.0~~95±41~~	103.0 ± 2.0~~99±44~~	0.22~~0.08~~
Duration of mechanical ventilation, (days) m+~~SD~~SE†	25.5 ± 1.1~~21±25~~	26.9 ± 1.0~~23±25~~	0.30~~0.21~~
Duration of oxygen supplementation, (days) m+~~SD~~SE†	59.8 ± 1.6~~52±38~~	67.4 ± 1.5~~61±37~~	0.0002~~<0.001~~
Continuous positive airway pressure, (days) m+SE~~†SD~~	17.1 ± 0.6~~16±14~~	17.0 ± 0.6~~16±14~~	0.94~~0.95~~
Nasal synchronized intermittent mandatory ventilation, (days) m+SE~~†SD~~	3.3 ± 0.3~~3±7~~	3.8 ± 0.3~~4±7~~	0.14~~0.06~~
Alive off mechanical ventilation by day 14, (days) – no. (%)~~m+SD~~	332/644 (51.6)~~331/643 (51)~~	326/655 (49.8)~~322/649 (50)~~	0.86~~0.50~~
Alive off mechanical ventilation by day 7, (days) – no. (%)~~m+SD~~	351/648 (54.2)	329/659 (49.9)	0.27

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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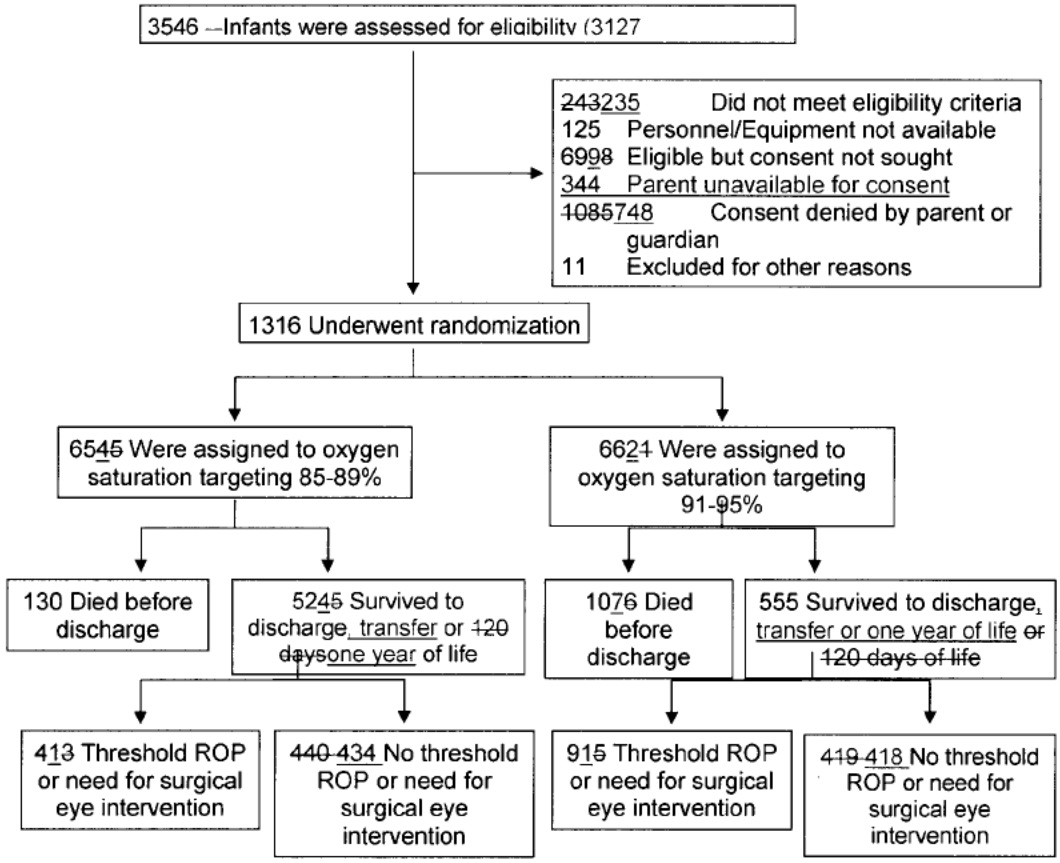
Figure 1

Comment [MG10]: We might need additional boxes at the bottom of the figure for those who survived but are missing the final ROP outcome: 49 in the low group and 46 in the high group.



* Excludes mothers who were screened who did not subsequently deliver a GDB (or SUPPORT) baby

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Figure 2 ~~Kaplan Meier plot~~Survivor Curve for ~~m~~Mortality ~~(from Marie)~~

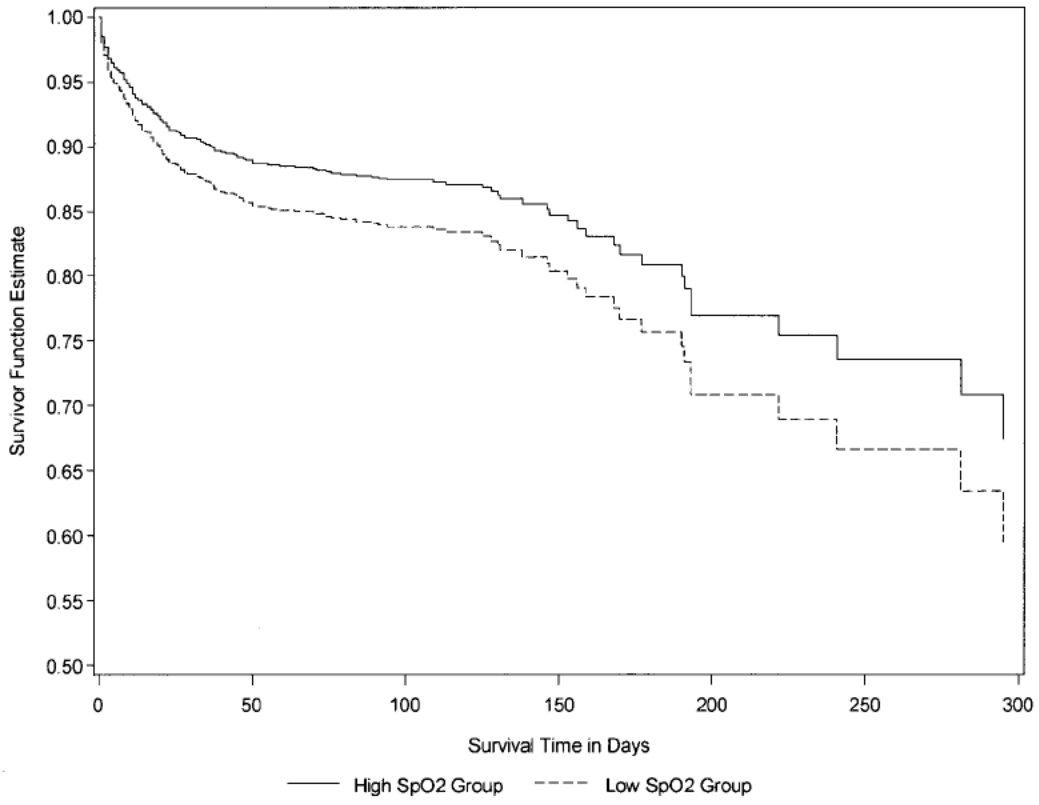

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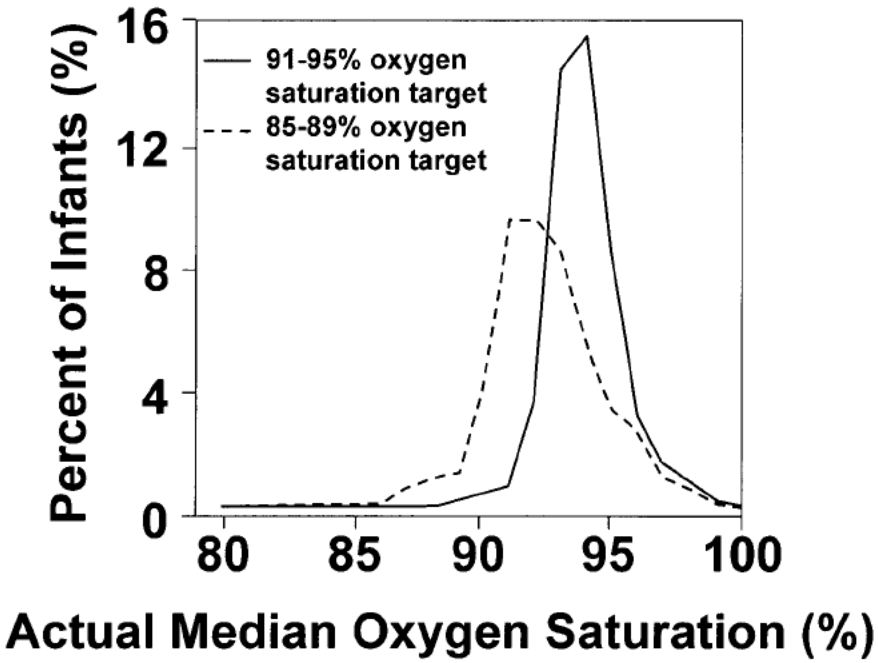
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Das, Abhik
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: cover letter for other DSMCs
Date: Monday, November 09, 2009 1:48:48 PM
Attachments: other DSMC letter.doc

This is what I came up with. Let me know if you have any comments.

Thanks

Abhik

Abhik Das, Ph.D.
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Telephone 301.230.4640 ▪ Fax 301.230.4647 ▪ www.rti.org

Hello _____:

I am writing to you on behalf of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), part of the U.S. National Institutes of Health, and the Data Safety and Monitoring Committee (DSMC) for the NICHD Neonatal Research Network.

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network in the United States of America. One of the factorial arms of this trial compares a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant no longer requires ventilatory support or oxygen. The oxygen saturation monitoring portion of the study is designed to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters that are calibrated to provide actual SpO2 values when the SpO2 is < 85% and > 95%. The primary outcome for this portion of the trial is survival free of severe retinopathy of prematurity (ROP), severe ROP being defined as threshold ROP and/or the need for surgical intervention.

This trial is now complete, and after their final planned look at the data, the independent DSMC for this trial recommended the sharing of some of this data with you, in your capacity as DSMC Chair for an ongoing randomized clinical trial that is using a similarly designed oximeter to compare a lower SpO2 range with a higher SpO2 range in a similar population of extremely premature babies. This data and an accompanying report are attached with this communication for your consideration as you review interim safety information for the trial you are monitoring.

Please note that since the study investigators are currently working on preparing final manuscripts for publishing the results of this trial, **the data that you are receiving should be treated with the strictest confidence** and not shared outside your DSMC, or with the investigators of the trial you are monitoring.

Sincerely

Abhik Das, Ph.D.
Principal Investigator
Data Coordinating Center for the NICHD Neonatal Research Network

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Gantz, Marie
Subject: SUPPORT DSMC data sharing
Date: Monday, November 09, 2009 12:43:26 PM
Attachments: info to share v2.doc

Rose:

The DSMC wanted the separation data for the SUPPORT SpO2 groups presented in a different manner. Marie has done that analysis, but we haven't sent it out to the group yet. Should we add that to the information we are sharing with the other DSMCs? It is found on the bottom of page 5 in the attached, through the figure on page 6.

Thanks

Abhik

Abhik Das, Ph.D.
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Selected Information from The Fourth Data Safety and Monitoring Committee Report for The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

CONFIDENTIAL

November 4, 2009

Prepared by the NICHD Neonatal Research Network Data Center at RTI International, Research Triangle Park, NC

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A. Methods and Procedures

Study Design

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (NRN). The individual factors to be tested are:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (≤ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant no longer requires ventilatory support or oxygen.

The oxygen saturation monitoring portion of the study is designed to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters that are calibrated to provide actual SpO2 values when the SpO2 is < 85% and > 95%. This methodology provides clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Primary Hypotheses

1) Relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks postmenstrual age (PMA).

2) Relative to infants managed with a higher SpO2 range, the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

Secondary Hypotheses

Use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decrease in mortality or neurodevelopmental impairment (NDI) at 18-22 months corrected age
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decrease in the percentage of infants who receive postnatal steroids for BPD
- A decreased incidence of BPD at 36 weeks PMA
- A decreased incidence of threshold ROP and/or the need for surgical intervention
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of intraventricular hemorrhage (IVH) and severe IVH
- A decreased incidence of periventricular leukomalacia (PVL)
- A decreased incidence of NDI at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up

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Study Population

Study subjects are infants of 24 0/7 to 27 6/7 weeks gestational age (GA) at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) are enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. There are 2 randomization strata, infants of 24 0/7 to 25 6/7 weeks GA, and infants of 26 0/7-27 6/7 weeks GA by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study is not powered to detect outcome differences between strata.

Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

Sampling Recruitment and Screening Procedures

Infants are recruited for this study by approaching parent(s) at the time of hospital admission when there is a perceived risk of premature delivery at 27 6/7ths weeks or less.

Sample Size

The required sample size for this trial was determined to be 1,310 to ensure 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. These results were based on observed prevalence of these outcomes in the Network Generic Data Base (GDB, a registry of all <1500 g births in the Network), and corrected for two primary outcomes (assumed significance level of 2%), for a clustering effect because of multiples being randomized to the same treatment, as well as for attrition. Note that this sample size is not sufficient to permit detection of interaction effects between the two treatments with reasonable power.

Randomization

Randomization is stratified by study site and gestational age group, occurs prior to delivery for consented deliveries, and is performed by utilizing specially prepared double-sealed envelopes. Deliveries are randomized as a unit, thus multiples, twins, triplets etc are randomized to the same arm of the trial. Appropriate sample size adjustments have been made to account for this clustering effect.

Study Intervention

The intervention begins after birth when the infant is given to the resuscitation team. The conduct of the resuscitation follows usual guidelines, and once stabilized, all Control infants in the Ventilation arm receive prophylactic/early surfactant (within 1 hour of age) whereas all

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Treatment infants are placed on CPAP/PEEP following stabilization and intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment is performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission. There are two ranges of SpO2 utilized during this trial. The Low target range is 85% to 89% and the High target range is 91% to 95%. The altered Pulse Oximeters (PO) display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO reads 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO displays 88% when the actual SpO2 is 91% and indicates 92% when the actual SpO2 is approximately 95%.

Interim Monitoring Plan

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion using interim monitoring boundaries. Efficacy is measured at approximately 25%, 50%, 75%, and 100% of outcome assessment. Primary outcomes are analyzed at these time points by statistically adjusting for familial clustering and stratification by gestational age stratum and center. To control for the inflation of Type I error associated with sequential testing, O'Brien-Fleming[1] boundaries are calculated using a Lan-DeMets[2] spending function. Safety is monitored at these time points as well using Pocock[3] boundaries for adverse event monitoring.

B. Selected Results

Enrollment

This is an extract from the report prepared for the final planned DSMC look at 100% of the primary outcome data for the SUPPORT Trial. As of February 2009, 1,316 infants have been enrolled in SUPPORT, exceeding the total expected enrollment of 1,310.

Treatment Compliance in Oxygen Saturation Arm

In the oxygen saturation arm, target saturation ranges are 85-89% and 91-95% for the Low and High SpO2 arms, respectively. **Table I** shows the percent of time infants on supplemental oxygen spent in various SpO2 ranges. Supplemental oxygen is defined as FiO2>.21 during the first 14 days of life (FiO2 is reported every two hours) or as documented oxygen use from day of life 15 through 36 weeks (oxygen use is recorded every 6 hours).

Time on supplemental oxygen	Oxygen saturation arm	Percent in narrow target 88-92 (Display)	Percent <84	Percent 84-96	Percent >96
Days of life 1-14	Low SpO2	19.7	11.8	76.2	12.0
	High SpO2	49.3	6.3	79.5	14.2
Day 15 to 36 wks	Low SpO2	15.5	15.4	67.1	17.6
	High SpO2	37.0	10.5	67.7	21.8

Table I Distribution of Time in SpO2 Display Ranges while on Supplemental Oxygen

Separation in Oxygen Saturation Arm **Table II** and **Figure I** address treatment separation in the Oxygen Saturation arm of the SUPPORT Trial. **Table II** shows the amount of time infants in

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each treatment group spend in room air. Only data from March 2006 to the present are included in Table 3.b, because since that time supplemental oxygen use has been recorded every two hours for day of life (DOL) 1-14 and every 6 hours thereafter. These data indicate some separation between the two treatment groups.

	DOL 1-14		DOL 15+	
	High SpO2	Low SpO2	High SpO2	Low SpO2
Hours in room air (hours in thousands)	35% (57/162)	46% (71/157)	35% (213/600)	46% (254/552)

Table II Percent of Time Spent in Room Air Since March 2006, by Treatment and Day of Life

Figure I shows the distribution of SpO2 values during time spent on supplemental oxygen for infants in the Low and High SpO2 target groups through 36 weeks PMA. There is modest separation between the groups, along with substantial overlap. The area under the overlapping portions of the curves is 85%. Thus, 15% of the area under each curve does not overlap the other.

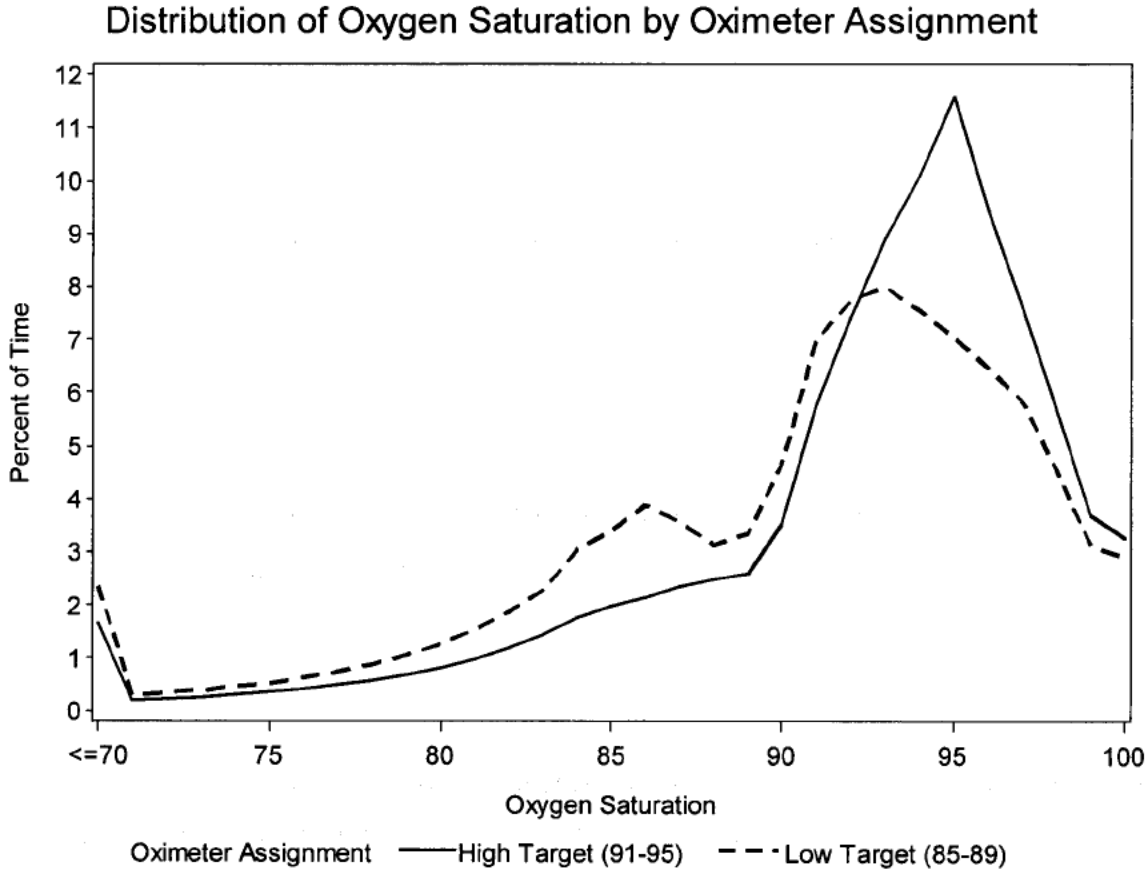

Figure I Percent of Time Spent at Each SpO2 Value for Infants in Low and High Target Groups (Includes only time on supplemental oxygen through 36 weeks PMA)

Upon presentation of the above results to the DSMC, the group requested additional information, which is presented below. Figure II below shows the median SpO2 for each infant,

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by oxygen saturation target group. A non-parametric Rank Sums test indicates that there is a statistically significant difference between medians of the two distributions ($p<0.0001$). The medians for infants in the low and high target SpO2 groups are 92% and 94%, respectively.

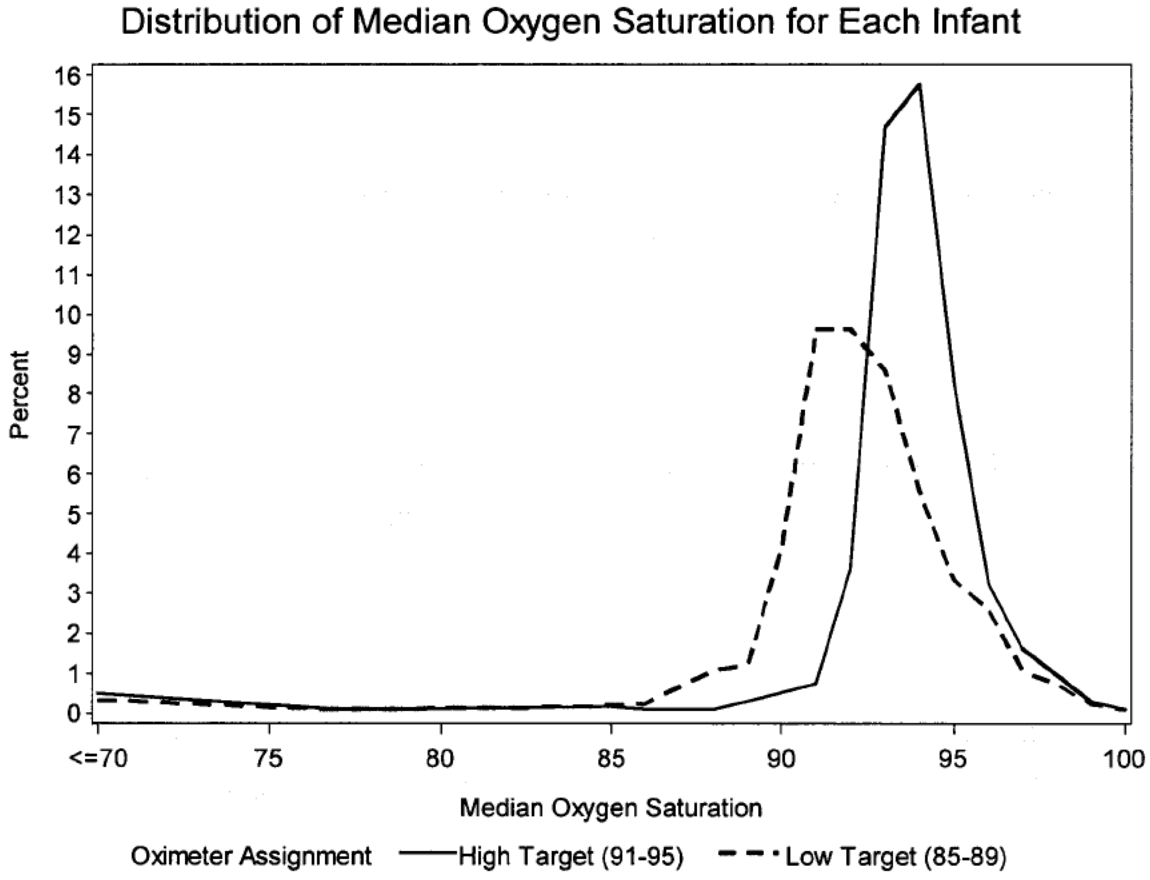

Figure II Infant-Level Median SpO2 Value, by Treatment

Mortality Information

Table III show the percent of infants in each treatment group who died during the course of the SUPPORT Trial. The table also displays adjusted p-values for statistical tests comparing the percent of infants who died in each level of the two treatment factors. The tests are adjusted for familial clustering due to multiple births and for stratification by center and gestational age group. There is a statistically significant difference in the death rate between treatments in the oxygen saturation arm, with higher mortality in the low SpO2 arm.

Outcome	Oxygen Saturation Arm		Adjusted P-value
	Low SpO2 (N=654)	High SpO2 (N=654)	
Death	20% (130/654)	16% (107/662)	0.0412

Table III Death in the Oxygen Saturation Arm

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Gestational age was a significant predictor of death in the tests presented in Table III ($p<0.0001$). **Table IV** presents the mortality information by gestational age stratum. Note that the 26-27 week gestational age stratum includes three infants born at 28 weeks gestational age.

Gestational Age Strata	Oxygen Saturation Arm		Adjusted P-value
	Low SpO2	High SpO2	
GA 24-25 weeks (N=565)	31% (85/276)	25% (73/289)	0.1225
GA 26-27 weeks (N=751)	12% (45/378)	9% (34/373)	0.1811

Table IV Death in the Oxygen Saturation Arm by Gestational Age Group

Cause of Death **Table V** lists causes of death by treatment and gestational age group to address safety concerns regarding RDS and other factors contributing to mortality.

Cause of Death	Low SpO2		High SpO2	
	24-25 wks (N=85)	26-27 wks (N=45)	24-25 wks (N=73)	26-27 wks (N=34)
RDS	27% (23/85)	18% (8/45)	29% (21/73)	29% (10/34)
BPD	9% (8/85)	13% (6/45)	12% (9/73)	3% (1/34)
Infection	19% (16/85)	20% (9/45)	18% (13/73)	24% (8/34)
NEC	20% (17/85)	13% (6/45)	12% (9/73)	15% (5/34)
CNS Insult	12% (10/85)	4% (2/45)	8% (6/73)	9% (3/34)
Immaturity	6% (5/85)	4% (2/45)	4% (3/73)	0% (0/34)
Other	7% (6/85)	27% (12/45)	16% (12/73)	21% (7/34)

Table V Cause of Death, by Oxygen Saturation Treatment and GA at Birth

1 O'Brien, P. C. and Fleming, T. R. (1979), A multiple testing procedure for clinical trials. Biometrics, 35, 549-556.

2 Reboussin, D. M., DeMets, D. L., Kim, K. and Lan, K. K. G. (2000), Computations for group sequential boundaries using the Lan-DeMets spending function method. Controlled Clinical Trials, 21, 190-207.

3 Pocock, S. J. (1977), Group sequential methods in the design and analysis of clinical trials. Biometrika, 64, 191-199.

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 12:31:28 PM

Fine

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 12:27 PM
To: 'Finer, Neil'; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Roger Faix; Brad Yoder (Bradley.yoder@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

Kurt has proposed an alternative for the CPAP/surf paper. As many of you are likely to recall, Ed Donovan organized the SUPPORT training and the video in 2004. Let me know if ED and Vivek can appear on the CPAP/surf paper.

Thanks
Rose

From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, November 09, 2009 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper
Importance: High

Hi Rose,
Personally, I would like to advocate that Ed Donovan and Vivek Narendran both be listed as Cincinnati authors on the CPAP Surfactant manuscript since Ed and Vivek did a lot to move forward the study up front and Vivek was instrumental during the trial. (Ed did a lot with initial start up and education, hosting the training, producing the training video, and was the Cincinnati PI at the beginning of the study). I would like to be listed as the author from Cincinnati on the Oxygen Saturation.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736-(b) (6)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
___X__ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript

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_____ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,

Just wondering,

Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.

Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

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However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org; Roger Faix; Bradley.yoder@hsc.utah.edu; kurt.schibler@cchmc.org; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 12:28:00 PM

Ok with me.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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Phone: 205 934 4680
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Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 11:27 AM
To: 'Finer, Neil'; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; Roger Faix; Brad Yoder (Bradley.yoder@hsc.utah.edu); Kurt Schibler [kurt.schibler@cchmc.org]; mcw3@case.edu; alaptook@WIHRI.org; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
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Importance: High

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From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, November 09, 2009 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper
Importance: High

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Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009

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Pager: 513-736-(b)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

See the request below -- **Please send me an email by the end of the day with for the following:**

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_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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Sent: Monday, November 09, 2009 6:10 AM
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Subject: Saturation paper

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Dale

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Ph. (707) 897-9063

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From: Wally Carlo, M.D.
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 12:17:36 PM

I have changed the primary outcome to severe ROP/death; that is how it was called in the clinicaltrials.gov record.

Let me know if there are any objections.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 09, 2009 10:45 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole

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subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Saturation paper
Date: Monday, November 09, 2009 12:01:02 PM

Hi Rose,
Yes, I would very much appreciate it!
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology, ML 7009
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
TEL: 513-636-3972
Pager: 513-736-(b)
E-mail: kurt.schibler@cchmc.org

On 11/9/09 11:56 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> May I send this choice to the subcommittee?
>
> ---
>
> **From**: Kurt Schibler <kurt.schibler@chmcc.org>
> **To**: Higgins, Rosemary (NIH/NICHD) [E]
> **Sent**: Mon Nov 09 11:47:53 2009
> **Subject**: Re: Saturation paper
>
> Hi Rose,
> Personally, I would like to advocate that Ed Donovan and Vivek Narendran both be listed as Cincinnati authors on the CPAP Surfactant manuscript since Ed and Vivek did a lot to move forward the study up front and Vivek was instrumental during the trial. (Ed did a lot with initial start up and education, hosting the training, producing the training video, and was the Cincinnati PI at the beginning of the study). I would like to be listed as the author from Cincinnati on the Oxygen Saturation.
> Thanks,
> Kurt
>
> Kurt Schibler, MD
> Associate Professor of Pediatrics
> Division of Neonatology, ML 7009
> Cincinnati Children's Hospital Medical Center
> 3333 Burnet Avenue
> Cincinnati, Ohio 45229
> TEL: 513-636-3972
> Pager: 513-736-(b) (6)
> E-mail: kurt.schibler@cchmc.org
>
> On 11/9/09 9:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>
> > See the request below -- **Please send me an email by the end of the day with for the following:**
> >
> > Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)
> > _____ Nirupama Laroia for both papers
> > ___X__ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
> > _____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

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Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

_____ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,

Just wondering,

Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.

Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

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However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Gantz, Marie
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 11:45:11 AM
Attachments: SPR O2 Sats 11 6 09 MG.doc

Wally,

Here are my edits for the PAS abstract. I am still concerned about just calling the primary outcome threshold ROP or death, as some of our infants who received surgery for ROP did not have a prior exam recorded with threshold ROP. My edits reflect one possible way of rephrasing the outcome.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'

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Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants.

W.A. Carlo for the SUPPORT Subcommittee of the NICHD Neonatal Research Network.

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce retinopathy without increasing adverse outcomes.

Objective

To test the hypothesis that a lower oxygen saturation target decreases severe ROP (threshold retinopathy of prematurity or need for surgical intervention) or deaths in extremely premature infants.

Methods

~~1316~~ Eligible infants ~~of~~ were $24^{0/7}$ to $27^{6/7}$ weeks gestation inborn at 20 centers of the NICHD Neonatal Research Network. 1316 were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters. The primary outcome was a composite of ~~threshold~~ severe ~~retinopathy of prematurity~~ROP ~~and~~/or death.

Comment [MG1]: 3 of the randomized infants were 28 0/7 weeks.

-

Results

~~Threshold~~ Severe ~~retinopathy~~ROP/death did not differ between the oxygen saturation target groups (Table). ~~Threshold~~ Severe ~~retinopathy~~ ROP was decreased (P<0.01~~5~~) in the lower oxygen

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saturation target group but death was more frequent (P<0.05, Table). Bronchopulmonary dysplasia (BPD) defined as o~~O~~xygen use at 36 weeks decreased in the lower oxygen saturation target group but death or ~~oxygen use~~BPD by the physiologic definition or oxygen use at 36 weeks~~/death~~ did not decrease. Other outcomes did not differ between the groups.

Conclusions

Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of ~~threshold retinopathy~~severe ROP/death but resulted in an increase in mortality that partially offset a decrease in ~~threshold retinopathy~~severe ROP. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term retinopathy benefits.

Table:

	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
~~Threshold retinopathy~~Severe ROP/death	171/605 (28.3)	198/616 (32.1)	0.90 (0.76,
Severe ROP~~Threshold retinopathy~~	43/483 (8.9)	95/514 (18.5)	0.51 (0.37,
Death before discharge	130/654 (~~20~~19.9)	107/662 (16.2)	1.27 (1.01, 1.60)
~~Bronchopulmonary dysplasia~~BPD by O_2 use at 36 weeks*	203~~2~~/540 (37.6)	265/568 (46.7)	0.82 (0.7
			0.93)~~0.81 (0.71,~~
			~~0.92)~~
~~Bronchopulmonary dysplasia~~BPD (O_2 use) or death by 36 weeks*	317/654	359/662	0.91 (0.8
	(48.5)~~316/654~~	(54.2)~~359/662~~	1.01)~~0.91 (~~

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	~~(48)~~	~~(54)~~	~~1.01)~~
~~Bronchopulmonary dysplasia~~BPD (physiologic) at 36 weeks*	205/540 (38.0)	237/568 (41.7~~2~~)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13.2)	81/640 (12.7~~3~~)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (1~~2~~1.9)	70/649 (1~~1~~0.8)	1.11 (0.82, 1.51)
Late onset sepsis	228/624 (3~~7~~6.5)	226/634 (35.6)	1.03 (0.89, 1.18)
Patent ductus arteriosus	307/641 (4~~8~~7.9)	324/648 (50.0)	0.96 (0.86, 1.07)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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From: Gantz, Marie
To: Das, Abhik; Danny Benjamin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: revision
Date: Monday, November 09, 2009 11:02:30 AM
Attachments: Empirical antifungals abstract for SPR_11 08 09 adrev MG.doc

---

I have added my edits to Abhik's. If there are subsequent drafts, would you please include me on the circulation list?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Das, Abhik
Sent: Monday, November 09, 2009 10:07 AM
To: 'Danny Benjamin'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie
Subject: RE: FW: revision

Suggested changes are attached. I tried to explain propensity scores a little more without increasing the amount of words.

Thanks

Abhik

From: Danny Benjamin [mailto:danny.benjamin@duke.edu]
Sent: Sunday, November 08, 2009 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]; 'Barbara Stoll'; Wallace, Dennis; Ronald N Goldberg; Zaterka-Baxter, Kristin; Cunningham, Meg; mcw3@cwru.edu; 'Nancy Miller'; Pablo.Sanchez@UTSouthwestern.edu; Huitema, Carolyn Petrie; Shankaran, Seetha; Rachel G Greenberg
Subject: Re: FW: revision

all, attached is the draft abstract for spr. i realize this is last minute, i apologize. given commitments for support, the analysis was just completed late this past week and the abstract needs to go to rose for approval tomorrow. please let me know if you have any edits.

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University Pediatrics
Chief, Division of Quantitative Sciences

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Director, DCRI Clinical Research Fellowship Program

2400 Pratt St.
Duke Clinical Research Institute Durham NC 27715
Ph: 919-668-8295; Fax: 919-681-9457

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Outcomes of eEmpirical antifungal therapy in extremely low birth weight infants: ~~Effect on mortality and neurodevelopmental outcome~~

[1,2]Rachel G. Greenberg MD, Marie Gantz PhD[3], [1,2]P. Brian Smith MD MHS, [1]C. Michael Cotten MD MHS, Rosemary Higgins MD [1,2]Daniel K. Benjamin Jr MD PhD and the Neonatal Research Network Candida Subcommittee

[1]Department of Pediatrics, Duke University, Durham, NC
[2]Duke University Clinical Research Institute, Durham, NC
[33]RTI International, Research Triangle Park, NC,
[4]National Institute Child Health Human Development Rockville, MD

Background: Invasive candidiasis is a leading cause of infection-related morbidity and mortality in premature infants. Empiric antifungal therapy (EAT) improves outcomes in adults at high risk for fungal infections, but no such studies have been performed in neonates.

Objective: To assess ~~the effect of~~mortality and morbidity ~~timing of empiric antifungal therapy~~outcomes upon receipt of EAT ~~on mortality and morbidity including NDI~~ among extremely low birth weight (ELBW) infants.

Methods: Demographic, clinical, and microbiological data were collected prospectively from infants ≤ 1000 g birth weight cared for at Neonatal Research Network sites. All infants had at least one positive culture for *Candida* from normally sterile body fluid, and had no evidence of congenital candidiasis. The primary outcome variables were survival and time to clearance of *Candida* from all sources. ~~Empirical antifungal therapy~~EAT was defined as receipt of a systemic antifungal on the day before or day on which the first positive culture for *Candida* was drawn (i.e., the day of initial sepsis work-up). ~~We used a logistic regression model for empirical antifungal therapy to determine a propensity score for each infant. The infants were divided into quartiles based on these propensity scores. We created logistic regression models stratified on these quartiles for each of the primary outcome variables using birth weight, age at first positive culture, gender, and presence or absence of empirical antifungal therapy as covariates.~~ Since babies receiving EAT may be systematically different from those who did not, we used propensity score modeling to stratify the analysies according to quartiles of the probability of receiving EAT. ~~Within each quartile, we used~~ Stratified logistic and survival regression ~~for~~models were created for death and days to clearance ~~each of the outcomes~~, with birth weight, age at first positive culture, gender, and presence or absence of EAT as covariates.

Results: 136 infants ~~with~~had invasive candidiasis and clinical data for the week preceding diagnosis were included ~~in the study~~. The median birth weight and gestational age were 680~~3~~ g and 24.9 weeks, respectively; 47 infants (35%) infants died prior to discharge; 39 infants received ~~empiric antifungal therapy~~EAT, and 97 did not. Mortality was comparable among babies who did or did not receive EAT (33% vs 35%). ~~Thirteen of the infants who received empiric antifungal therapy died (33%), and 34 infants who did not receive empiric antifungal therapy (35%) died. The~~For the 96 infants who obtained clearance of infection during the study, median [IQR] time to clearance ~~of infection~~ was 6 [4-14] days. In logistic regression analysis stratified by propensity score quartiles, lower birth weight ($p<0.001$) and male sex ($p=0.03$) were associated with decreased survival. However, ~~presence or absence of empirical antifungal therapy~~EAT was not associated with survival ($p=0.31$); nor was ~~empirical therapy~~it associated with decreased time to clearance of *Candida*.

Conclusions: The use of empiric antifungal therapy in ELBW infants with candidiasis was not associated with increased survival or decreased time to clearance of infection in this cohort of infected infants. The difference in relative benefit observed in older patients compared to these infants may relate to sample size or the non-randomized nature of our study ~~design that did not include randomization~~.

Comment [AD1]: 'Effect' implies causation, and I would avoid using that word.

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Comment [MG2]: 137 babies had candida, but only 136 had the clinical data we needed for the analysis. Only 116 had full data and were included in the PS analyses.

Comment [AD3]: This is just among those who received EAT, or in the whole sample?

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper
Date: Monday, November 09, 2009 10:57:21 AM

See below

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 09, 2009 9:22 AM
To: 'Finer, Neil'; 'wrich@ucsd.edu'; mcw3@case.edu; wacarlo@uab.edu; Roger Faix; alaptook@WIHRI.org; Kurt Schibler [kurt.schibler@cchmc.org]; 'Nancy Newman'; Gantz, Marie; Das, Abhik; Brad Yoder (Bradley.yoder@hsc.utah.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Saturation paper
Importance: High

See the request below -- **Please send me an email by the end of the day with for the following:**

Rochester authorship (Dale has had significant responsibility for the ROP portion of the manual, forms, data collection, answering questions along the way for the trial, and general input into the ROP issues)

_____ Nirupama Laroia for both papers
_x____ Nirupama Laroia for both papers + Dale Phelps for saturation manuscript
_____ Nirupama Laroia for CPAP surf paper + Dale Phelps for saturation manuscript

Also, one other issue has come to my attention – Kurt Schibler is one the subcommittee but is only on one of the papers. Let me know if you both he and Vivek should appear in the mast head for the CPAP/surf paper

__x___ Kurt for both papers
_____ Kurt for only saturation paper

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 09, 2009 8:30 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Saturation paper

Hi Dale:

I got he list from Rose and the Subcommittee. I will check with them.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street

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525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 09, 2009 6:10 AM
To: Wally Carlo, M.D.
Subject: Saturation paper

Hi Wally,
Just wondering,
Did you intend to have me listed as a co-author on the saturation paper? I received your note sent to 'all authors'.

At present, I am listed only as the Center PI at Rochester in the Biolerplate.
Rochester's protocol PI for SUPPORT was Nirupama Laroia, so she is appropriately listed as the author from Rochester.

However, I have carried a significant responsibility for the ROP data form, training, instructions, monitoring, etc. for the ROP primary outcome -- I think we could justify adding me to the authors list.

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Das, Abhik
To: Danny Benjamin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: FW: revision
Date: Monday, November 09, 2009 10:08:16 AM
Attachments: Empirical antifungals abstract for SPR_11 08 09 adrev.doc

Suggested changes are attached. I tried to explain propensity scores a little more without increasing the amount of words.

Thanks

Abhik

From: Danny Benjamin [mailto:danny.benjamin@duke.edu]
Sent: Sunday, November 08, 2009 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]; 'Barbara Stoll'; Wallace, Dennis; Ronald N Goldberg; Zaterka-Baxter, Kristin; Cunningham, Meg; mcw3@cwru.edu; 'Nancy Miller'; Pablo.Sanchez@UTSouthwestern.edu; Huitema, Carolyn Petrie; Shankaran, Seetha; Rachel G Greenberg
Subject: Re: FW: revision

all, attached is the draft abstract for spr. i realize this is last minute, i apologize. given commitments for support, the analysis was just completed late this past week and the abstract needs to go to rose for approval tomorrow. please let me know if you have any edits.

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University Pediatrics
Chief, Division of Quantitative Sciences
Director, DCRI Clinical Research Fellowship Program

2400 Pratt St.
Duke Clinical Research Institute Durham NC 27715
Ph: 919-668-8295; Fax: 919-681-9457

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Outcomes of eEmpirical antifungal therapy in extremely low birth weight infants~~: Effect on mortality and neurodevelopmental outcome~~

[1,2]Rachel G. Greenberg MD, Marie Gantz[3], [1,2]P. Brian Smith MD MHS, [1]C. Michael Cotten MD MHS, Rosemary Higgins MD [1,2]Daniel K. Benjamin Jr MD PhD and the Neonatal Research Network Candida Subcommittee

[1]Department of Pediatrics, Duke University, Durham, NC
[2]Duke University Clinical Research Institute, Durham, NC
[33]RTI International, Research Triangle Park, NC,
[4]National Institute Child Health Human Development Rockville, MD

Background: Invasive candidiasis is a leading cause of infection-related morbidity and mortality in premature infants. Empiric antifungal therapy (EAT) improves outcomes in adults at high risk for fungal infections, but no such studies have been performed in neonates.

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Results: 136 infants had invasive candidiasis and were included in the study. The median birth weight and gestational age were 683 g and 24.9 weeks, respectively; 47 infants (35%) infants died prior to discharge; 39 infants received empiric antifungal therapy, and 97 did not. Mortality was comparable among babies who did or did not receive EAT (33% vs 35%). ~~Thirteen of the infants who received empiric antifungal therapy died (33%), and 34 infants who did not receive empiric antifungal therapy (35%) died.~~ The median [IQR] time to clearance of infection was 6 [4-14] days. In logistic regression analysis stratified by propensity score quartiles, low birth weight ($p<0.001$) and male sex ($p=0.03$) were associated with decreased survival. However, presence or absence of empirical antifungal therapy was not associated with survival ($p=0.31$); nor was ~~empirical therapy~~it associated with decreased time to clearance of *Candida*.

Conclusions: The use of empiric antifungal therapy in ELBW infants with candidiasis was not associated with increased survival or decreased time to clearance of infection in this cohort of infected infants. The difference in relative benefit observed in older patients compared to these infants may relate to sample size or the non-randomized nature of our study ~~design that did not include randomization~~.

Comment [AD1]: 'Effect' implies causation, and I would avoid using that word.

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Comment [AD2]: This is just among those who received EAT, or in the whole sample?

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From: Gantz, Marie
To: Das, Abhik; Finer, Neil
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 9:45:34 AM
Attachments: CPAP PAS adrev MG.doc

I have added my edits to Abhik's.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Das, Abhik
Sent: Monday, November 09, 2009 9:27 AM
To: Finer, Neil
Cc: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: Oxygen Saturation paper for your comments.

Neil:

Some suggested editorial changes are attached, that cuts down on the words a little bit. I have expressed my reservations about the boldness of the conclusion before; so I won't repeat that again! I can live with it if it is acceptable to the subcommittee and the steering committee.

Thanks

Abhik

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, November 08, 2009 11:26 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Hi Neil:

Here are a few suggestions on the abstract.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

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619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 9:48 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I do not think that the abstracts will fit if we add all the subcommittee members - I am at 100.7% with this version Please review
Neil

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Cc: Marsha Sumner
Subject: Re: Oxygen Saturation paper for your comments.

If you can fit more authors, it is fine

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Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 17:18:45 2009

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Rose:

OK?

Wally

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Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf On both Abstracts I would like at least you and me as authors and then whatever follows I will put Finer, Carlo, you can do the flip side I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

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Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

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First Author: Neil N Finer

File Number: 751689

Presenting Author: Neil N Finer

Responsible Author: Neil N Finer

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Neiul n Finer MD

Formatted: Italian (Italy)

Department/Institution/Address: Department of Pediatrics, Division of Neonatology,, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812 **E-mail:** nfiner@ucsd.edu

---

Responsible Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Responsible Author E-mail: nfiner@ucsd.edu

Responsible Author Declaration:
As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, 402 Dickinson St., MPF 1-140 Department of Pediatrics, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Presenter E-mail: nfiner@ucsd.edu

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The presenting author is member of these Alliance Societies:

Is Presenting Author a Trainee? No, Not a Trainee

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Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

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Awards Applied for:

Consider for PAS Travel Grant Award: No

Sponsoring Member for PAS Abstracts
Sponsored by: Neil Norman Finer,
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring societies:
Society for Pediatric Research
Academic Pediatric Association

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants –The SUPPORT Trial

Neil N Finer, MD, Waldemar A Carlo, MD and the Neonatal Research Network of the NICHD.
[1]Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, San Diego, Ca, United States and [2]Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States.

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Objective: The SUPPORT Trial was designed to compare early CPAP with early surfactant in ELBW infants.

Design/Methods: ~~The~~ SUPPORT ~~Trial~~study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths ~~weeks~~ to 27 6/7ths weeks. Infants were randomized to either CPAP initiated in the delivery room, and ~~were~~ subsequently treated using a protocol driven limited ventilator strategy, or to. ~~Infants randomized to surfactant, were~~ being intubated and receiving~~ed~~ surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ~~ranges of~~target SpO2 ranges while receiving supplemental oxygen

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced at ~~49~~48.7% in the CPAP group versus 54.1% in the surfactant group, (RR 0.91, 95% CI 0.83, 1.01, p=0.07 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (243.9% vs 32.1%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). Overall, more CPAP infants were alive and off mechanical ventilation by day 7, (55.3% vs 49~~8~~.8%, p=0.01~~1~~) and fewer required intubation (83.1% vs ~~100~~99.7%, P<0.0001) or post natal steroids for BPD (7.2% vs 13.2%, p<~~=~~.0.0005). There was no significant difference in the occurrence of air leaks in the first 14 days, severe intraventricular hemor~~h~~rhage, medical or surgical necrotizing enterocolitis, or patent ductus arteriosus requiring surgery.

Conclusions: Compared with randomization to surfactant within 1 hour of birth, ~~ELBW~~ infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse

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neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Das, Abhik
To: Finer, Neil; Wally Carlo, M.D.
Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 9:32:54 AM

Sounds reasonable to me.

Thanks

Abhik

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 9:06 PM
To: Wally Carlo, M.D.
Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: Re: Oxygen Saturation paper for your comments.

I agree with using decimals
Neil

Sent from my iPhone

On Nov 8, 2009, at 2:38 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> ALL:
>
> I have a suggestion. Because our sample size is much larger that 100
> per
> group and closer to 1000 (as we all know), we should consider using a
> decimal point in the percentages. The reason is that rounding to full
> percentages obscures important information. For example, a close to 3%
> difference in mortality between the CPAP vs int/surf group is
> rounded to
> 4% but is not statistically significant. The difference of 4% in the
> mort of the sat groups is statistically sig. The other reason for
> adding
> a decimal is for more precise estimate of the NNT.
>
> Let me know what you think so we do it the same way on both papers.
>
> Wally
>
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
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> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Gantz, Marie [mailto:mgantz@rti.org]
> Sent: Sunday, November 08, 2009 2:39 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo,
> M.D.; Das, Abhik; wrich@ucsd.edu
> Subject: RE: Oxygen Saturation paper for your comments.
>
> Attached is the Oxygen Saturation paper with my edits and comments. I
> have updated all numbers and p-values. I have added to the methods
> section on statistical analysis, and I have added the survival
> analysis.
> Instead of using Kaplan-Meier analysis I have used Cox regression in
> order to adjust for stratification and clustering as in the other
> analyses. The results were similar, although the difference in the
> survival curves was significant (p=0.045) after adjustment and
> non-signficant in the KM analysis without the adjustments. See
> attached
> for the two survival curves for comparison.
>
> I will also update all numbers in the CPAP paper and send that out as
> well.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Sunday, November 08, 2009 3:06 PM
> To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz,
> Marie;
> 'wrich@ucsd.edu'
> Cc: 'MSumner@peds.uab.edu'
> Subject: Re: Oxygen Saturation paper for your comments.
>
> I think neil and wally on behalf of the support subcommittee of the
> nichd nrn is fine. If space permits, marie and wade can be added.
> Limitation in author number was instituted because the authors were
> taking up to 25 percent of alloted space.
> I need the abstract in the next day or so for nichd clearance.
> Thanks
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary
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> Sent: Sun Nov 08 13:27:55 2009
> Subject: RE: Oxygen Saturation paper for your comments.
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> Hi Wally
> I am working on the abstract for CPAP and Surf
> On both Abstracts I would like at least you and me as authors and then
> whatever follows
> I will put Finer, Carlo, you can do the flip side
> I don't know how many authors the NRN requires on abstracts but we
> will
> have 2 anyway- if we can do more I would put Wade, Rose and Marie.
> Let me know
> Neil
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 3:46 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie;
> Finer, Neil; Rich, Wade
> Cc: Marsha Sumner
> Subject: FW: Oxygen Saturation paper for your comments.
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> The paper and the PAS draft are enclosed.
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> From: Wally Carlo, M.D.
> Sent: Friday, November 06, 2009 4:33 PM
> To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu';
> 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
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Subject: RE: Oxygen Saturation paper for your comments.
Date: Monday, November 09, 2009 9:27:35 AM
Attachments: CPAP PAS adrev.doc

Neil:

Some suggested editorial changes are attached, that cuts down on the words a little bit. I have expressed my reservations about the boldness of the conclusion before; so I won't repeat that again! I can live with it if it is acceptable to the subcommittee and the steering committee.

Thanks

Abhik

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, November 08, 2009 11:26 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Hi Neil:

Here are a few suggestions on the abstract.

Wally

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First Author: Neil N Finer

File Number: 751689

Presenting Author: Neil N Finer

Responsible Author: Neil N Finer

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Neiul n Finer MD

Formatted: Italian (Italy)

Department/Institution/Address: Department of Pediatrics, Division of Neonatology,, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812 **E-mail:** nfiner@ucsd.edu

---

Responsible Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Responsible Author E-mail: nfiner@ucsd.edu

Responsible Author Declaration:
As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, 402 Dickinson St., MPF 1-140 Deoartment of Pediatrics, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Presenter E-mail: nfiner@ucsd.edu

Formatted: Italian (Italy)

The presenting author is member of these Alliance Societies:

Is Presenting Author a Trainee? No, Not a Trainee

Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

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Awards Applied for:

Consider for PAS Travel Grant Award: No

Sponsoring Member for PAS Abstracts
Sponsored by: Neil Norman Finer,
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring societies:
Society for Pediatric Research
Academic Pediatric Association

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants –The SUPPORT Trial

Neil N Finer, MD, Waldemar A Carlo, MD and the Neonatal Research Network of the NICHD.
[1]Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, San Diego, Ca, United States and [2]Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States.

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Objective: The SUPPORT Trial was designed to compare early CPAP with early surfactant in ELBW infants.

Design/Methods: ~~The~~ SUPPORT ~~Trial~~~~study~~ was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths ~~weeks~~ to 27 6/7ths weeks. Infants were randomized to either CPAP initiated in the delivery room, and ~~were~~ subsequently treated using a protocol driven limited ventilator strategy, or to. ~~Infants randomized to~~ surfactant, ~~were~~ being intubated and receiving~~ed~~ surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced at 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.83, 1.01, p=0.07 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). Overall, more CPAP infants were alive and off mechanical ventilation by day 7, (55% vs 49%, p=0.01~~1~~) and fewer required intubation (83% vs 100%, P<0.0001) or post natal steroids for BPD (7% vs 13%, p<.0.0005). There was no difference in the occurrence of air leaks in the first 14 days, severe intraventricular~~t~~ hemor~~h~~rhage, medical or surgical necrotizing enterocolitis, or patent ductus arteriosus requiring surgery.

Conclusions: Compared with randomization to surfactant within 1 hour of birth, ~~ELBW~~ infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse

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neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From:	Pablo Sanchez
To:	Danny Benjamin; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	mcw3@cwru.edu; Archer, Stephanie (NIH/NICHD) [E]; Ronald N Goldberg; Rachel G Greenberg; Seetha Shankaran; "Barbara Stoll"; Abhik Das; Dennis Wallace; Kristin Zaterka-Baxter; Meg" "Cunningham; Carolyn Petrie" "Huitema; Nancy Miller
Subject:	Re: FW: revision
Date:	Monday, November 09, 2009 8:07:24 AM
Attachments:	Empirical antifungals abstract for SPR 11.08.09-pjs.doc

hi danny--my comments, etc--pablo

>>> Danny Benjamin <danny.benjamin@duke.edu> 11/8/09 11:39:03 AM >>>
all, attached is the draft abstract for spr. i realize this is last minute, i apologize. given commitments for support, the analysis was just completed late this past week and the abstract needs to go to rose for approval tomorrow. please let me know if you have any edits.

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University Pediatrics
Chief, Division of Quantitative Sciences
Director, DCRI Clinical Research Fellowship Program

2400 Pratt St.
Duke Clinical Research Institute Durham NC 27715
Ph: 919-668-8295; Fax: 919-681-9457

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Empirical antifungal therapy in extremely low birth weight (ELBW) infants: Effect on mortality and neurodevelopmental outcome

[1,2]Rachel G. Greenberg MD, Marie Gantz[3], [1,2]P. Brian Smith MD MHS, [1]C. Michael Cotten MD MHS, Rosemary Higgins MD [1,2]Daniel K. Benjamin Jr MD PhD and the Neonatal Research Network Candida Subcommittee

[1]Department of Pediatrics, Duke University, Durham, NC
[2]Duke University Clinical Research Institute, Durham, NC
[33]RTI International, Research Triangle Park, NC,
[4]National Institute Child Health Human Development Rockville, MD

Background: Invasive candidiasis is a leading cause of infection-related morbidity and mortality in premature infants. Empirical antifungal therapy improves outcomes in adults who at high risk for fungal infections, but similar evidence is lacking in neonates~~no such studies have been performed in neonates~~.

Objective: To assess the effect of timing of empirical antifungal therapy on mortality and morbidity including NDI (need to spell out or change the title and include the abbreviation there) among ~~extremely low birth weight~~ (ELBW) infants.

This does not make too much sense to me—"timing" of empiricial therapy? By definition, it is early before the culture results are known –I think that it should be the effect of initiation of empirical antifungal therapy…otherwise, it would just be the timing of antifungal therapy…

Methods: Demographic, clinical, and microbiological data were collected prospectively from infants ≤ 1000 g birth weight cared for at Neonatal Research Network sites. All infants had at least one positive culture for *Candida* from a normally sterile body fluid ~~,~~ and ~~had~~ no evidence of congenital candidiasis. The primary outcome variables were survival and time to clearance of *Candida* from all sources (body fluids or sites?) (but in the title you have neurodev outcome and in objective, NDI??) . Empirical antifungal therapy was defined as receipt of a systemic antifungal agent on the day on which the first positive culture for *Candida* was obtained ~~drawn~~ (i.e., the day of initial sepsis evaluation ~~work-up~~and before culture result known). ~~We used a~~A logistic regression model for empirical antifungal therapy was used to determine a propensity score for each infant. The infants were divided into quartiles based on these propensity scores (should you state something about this??). We created logistic regression models stratified on these quartiles for each of the primary outcome variables (what are these—survival and time to clearance only?) using birth weight, age at first positive culture, gender, and presence or absence of empirical antifungal therapy as covariates. Center? How does it play into this?

Results: 136 infants had invasive (what is this definition? Probably would not state it as such but rather had a positive culture and state the sites—some may have been catheter-associated and would not really call "invasive" if it clears with pulling it and no peripheral one positive --would prefer systemic candidiasis) candidiasis (all blood? How many other sites? Blood, #, CSF #, urine, #) and were included in the study. The median birth weight and gestational age were 683 g and 24.9 weeks, respectively; 47 infants (35%) infants died prior to discharge (related to candida?) ; 39 infants received empirical antifungal therapy, and 97 did not. Thirteen (33%) of the infants who received empirical antifungal therapy died ~~(33%)~~, while ~~and~~ 34 (35%) infants who did not receive empirical antifungal therapy ~~(35%)~~ died. The median [IQR] time to clearance of infection was 6 [4-14] days –did this differ? It's part of your interested outcome. In logistic regression analysis stratified by propensity score quartiles, low birth weight (how is this defined?) ($p<0.001$) and male sex ($p=0.03$) were associated with decreased survival.

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However, presence or absence of empirical antifungal therapy was not associated with survival (p=0.31), nor was empirical therapy associated with decreased time to clearance of *Candida*. From the propensity scoring/logistic regression analysis? you state this before and could just add the p values ....

Your title has neurodevelopmental outcome and you later mention NDI, but there is nothing here on this—need to delete its reference if you did not look at it—or else need to comment on it

Conclusions: The use of empirical antifungal therapy in ELBW infants with systemic candidiasis was not associated with increased survival or decreased time to microbiological clearance of infection in this cohort of infected infants. The difference in relative benefit observed in older patients compared to these infants may relate to sample size or study design that did not include randomization.

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From: Phelps, Dale
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting
Date: Monday, November 09, 2009 5:44:09 AM
Attachments: SPR O2 Sats .dlp edits.doc

Hi Wally,
I attach some small edits aimed at shortening your abstract. I am ok with the abstract as edited... see what I did with the definition of threshold ROP.

I have more comments and thoughts for the manuscript, as I am not as comfortable with that yet. I just wanted to get the PAS abstract to you because I know the deadline is the 9th.

By the way, your letter is addressed to the subcommittee members, but I don't think they are listed on the "To" line. Perhaps you were just sending this out in split mailings.

Dale

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 12:47 PM
To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT Subcommittee Meeting

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

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Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants.

W.A. Carlo for the SUPPORT Subcommittee of the NICHD Neonatal Research Network.

Background

Non randomized studies suggest ~~that~~ the incidence of retinopathy of prematurity(ROP) decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce ROP~~retinopathy~~ without increasing adverse outcomes.

Objective

To test the hypothesis that a lower oxygen saturation target decreases severe ROP~~threshold retinopathy~~ and/or death~~s~~ in extremely premature infants.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters. The primary outcome was a composite of Type 1 threshold ROP~~retinopathy of prematurity~~ and/or death.

-

Results

Threshold ROP~~retinopathy~~/death did not differ between the oxygen saturation target groups (Table). Threshold ROP~~retinopathy~~ was decreased ($P<0.05$) in the lower oxygen saturation target group but death was more frequent ($P<0.05$, Table). Oxygen use at 36 weeks decreased in the

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lower oxygen saturation target group but oxygen use by the physiologic definition ~~or~~ of oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups.

Conclusions

Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of threshold ROP~~retinopathy~~/death but ~~resulted in~~ an increase in mortality ~~that~~ partially offset a decrease in threshold ROP ~~retinopathy~~. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term ROP~~retinopathy~~ benefits.

Table:

	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)

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* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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From:	Phelps, Dale
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; Nancy Newman; Susie Buchter; Brenda Morris; Laroia, Nirupama; Sood, Beena; Shahnaz Duara; Michael O`Shea; Anthony Piazza; vineet.bhandari@yale.edu; Vivek.Narendran@cchmc.org; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; Av Fanaroff; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Wally Carlo; cotte010@mc.duke.edu; Dennis Wallace; Edward Bell; Ed Donovan; Ehrenkranz@Yale. Edu>; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michele Walsh-Sukys; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Ken Poole; Roger Faix; Duke. Edu>.; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Jon Tyson; VanMeurs, Krisa
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Carolyn Petrie
Subject:	RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date:	Monday, November 09, 2009 4:26:16 AM

Thank you for sending the MS and tables Neil,
I have reviewed these, and have some general comments, and have also will forward a track changes version for minor things to address.

Overall, it reads well and is carefully considered. Please consider the following which I feel should be addressed:

1. The CONSORT statement for reporting clinical trials 'requires' a Figure 1 flow sheet that shows what happened to the enrolled infants. (The pulse oximetry paper has one of these that would be more simple for the BPD paper.

2. To either the flow sheet, or to the Table of baseline characteristics, I feel strongly that we have to show the proportion of each group that was randomized to the low sat (or high sat) group, within the two strata would be best. While you are not analyzing an interaction, the reader has to be able to confirm how the randomization worked out in the 2x2 design.

3. It seems very odd (coincidental), that the death rates in the CPAP vs. surfactant groups were identical to the high vs. low sats (16% vs. 20%). Please verify.

4. The small maldistribution of males in the CPAP vs. Surf groups are similar to the maldistribution of males in the high vs. low sats. Again, it seems pertinent to know the distribution in the four cells of the 2x2 table.

I guess I'm getting down to being concerned that the readers/reviewers are going to chafe at having only half a story, and no effort whatsoever to look at any interaction. Just because we don't have the power to detect an interaction does not mean that we are not permitted to look.

Or was the design only for convenience of doing two experiments at one time on the same babies and no a priori thought that there MIGHT be an interaction?

Were the BPD outcomes adjusted for which saturation stratum the infant was in? If you tell me "No, because we stratified randomization for CPAP/surf on the saturation group", then I ask you why did you adjust for center? or gestation?

5. reference #18 is incorrect. This is the design manuscript. Type 1 and Type 2 ROP were not defined until post hoc in writing up the

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outcomes of the trial. The one you want is:

ETROP Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology 2003; 121(12):1684-1694.

Other less substantive edits to follow when I get a chance.
Dale

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Saturday, November 07, 2009 9:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; Laroia, Nirupama; Sood, Beena; Shahnaz Duara; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); Av Fanaroff; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo; cotte010@mc.duke.edu; Dennis Wallace; Edward Bell; Ed Donovan; Ehrenkranz@Yale. Edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh-Sukys; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Ken Poole; Roger Faix; Duke. Edu>;; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Jon Tyson; VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Carolyn Petrie
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Here are the Tables as Word 2004 docs
Neil

On 11/7/09 9:09 AM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Again
The previous version was unreadable by most - Sorry for that Here is a Word doc that I hope all can read Neil

On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 - 4 PM - call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutesof Health 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 11:25:57 PM
Attachments: First Author.doc

Hi Neil:

Here are a few suggestions on the abstract.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 9:48 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

I do not think that the abstracts will fit if we add all the
subcommittee members - I am at 100.7% with this version
Please review
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, November 08, 2009 2:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

Should we try to put the whole subcommittee?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335

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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, November 08, 2009 4:22 PM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'adas@rti.org'; 'mgantz@rti.org'; 'wrich@ucsd.edu'
Cc: Marsha Sumner
Subject: Re: Oxygen Saturation paper for your comments.

If you can fit more authors, it is fine

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>
Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 17:18:45 2009
Subject: RE: Oxygen Saturation paper for your comments.

Hi Neil:

That sounds fine to me. Usually we have not put too many authors. We can put you and me and then "and the SUPPORT Subcommittee of the NICHD Neonatal Research Network".

Rose:

OK?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)
-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 12:28 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Rich, Wade
Cc: Marsha Sumner
Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf
On both Abstracts I would like at least you and me as authors and then

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whatever follows
I will put Finer, Carlo, you can do the flip side
I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
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-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics

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First Author: Neil N Finer **File Number:** 751689

Presenting Author: Neil N Finer

Responsible Author: Neil N Finer

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Neiul n Finer MD

Formatted: Italian (Italy)

Department/Institution/Address: Department of Pediatrics, Division of Neonatology,, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

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Responsible Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

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Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

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Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial In Extremely Low Birth Weight Infants –The SUPPORT Trial

Neil N Finer, MD, Waldemar A Carlo, MD and the Neonatal Research Network of the NICHD.
[1]Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, San Diego, Ca, United States and [2]Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States.

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Objective: The SUPPORT Trial was designed to compare early CPAP with early surfactant in ELBW infants.

Design/Methods: The SUPPORT Trial~~study~~ was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced at 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.83, 1.01, p=0.07 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). Overall, more CPAP infants were alive and off mechanical ventilation by day 7, (55% vs 49%, p=0.01~~1~~) and fewer required intubation (83% vs 100%, P<0.0001) or post natal steroids for BPD (7% vs 13%, p<.0.0005). There was no difference in the occurrence of air leaks in the first 14 days, severe intraventricular~~t~~ hemorr~~h~~hage, medical or surgical necrotizing enterocolitis, or patent ductus arteriosus requiring surgery.

Conclusions: Compared with randomization to surfactant within 1 hour of birth, ~~ELBW~~ infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse

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neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Wally Carlo, M.D.
To: Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts
Date: Sunday, November 08, 2009 9:39:26 PM

Marie:

Thanks!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Sunday, November 08, 2009 8:36 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts

Neil,

Here is your paper with updated numbers and my edits, as well as the three source tables I have produced before, now with adjusted p-values and RRs where appropriate.

Will there also be a table showing the primary outcomes? Right now the variables covered in the text and tables don't seem to match completely.

I saw the messages about adding a decimal to the percentages, but not before I had run this version. I will re-run the CPAP and SpO2 paper tables tomorrow with the decimal.

Marie

Marie Gantz, Ph.D.
Research Statistician
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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 04, 2009 1:02 PM

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To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: Re: manuscripts

Hi Rose
Here is the SUPPORT CPAP Surf paper with Tables for circulation
Neil
On 11/4/09 9:33 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

Hi,
Can you send me the updated versions of the manuscripts for distribution to the SC members and co-authors by Monday?? Have you received input from the subcommittee members?

Thanks
Rose

Rosemary D. Higgins, MD
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From: Gantz, Marie
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts
Date: Sunday, November 08, 2009 9:35:47 PM
Attachments: SUPPORT CPAP Manuscript - Network Version Word Nov 6 09_MG.doc
Tables Nov 06 09 (MG).docx
T2 Other Outcomes - 08NOV09.doc
T3 BPD Outcomes - 08NOV09.doc
T1 Patient Description - 08NOV09.doc

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Marie Gantz, Ph.D.
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Sent: Wednesday, November 04, 2009 1:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: Re: manuscripts

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Rosemary D. Higgins, MD

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Word count:

Abstract: 250

Manuscript: 3079

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while ~~in the NICU and~~ receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.83~~2~~, 1.01~~0~~, p=0.07~~6~~ when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.011~~9~~) and fewer required intubation or post natal steroids for BPD, (p<.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP for preterm infants with RDS in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] ~~The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation.~~ Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[14] However, the surfactant trials preceded widespread use of antenatal corticosteroids to promote lung maturation and the placebo groups did not received mechanical ventilation which could be injurious.

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group ~~(9.1~~(9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent

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with the findings of an earlier meta analysies[44], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006~~) with~~) with no statistically significant difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT Trial~~study~~ was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. (already stated)~~These results will be separately reported~~.

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The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27~~8~~ weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, -and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece ~~resuscitator or~~resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: ~~Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol,~~ CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% for one hour, an arterial $PaCO_2$ > 65 torr ~~documented on a single blood gas within one hour of intubation~~, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU ~~standardpractice~~standard practice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ ~~15 bpm~~15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and ~~be~~ hemodynamically ~~stable with~~stable without

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~~no~~ evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data)~~, and~~, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61~~% using~~% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

Comment [MG1]: I believe the SpO2 paper says 1310. They should agree.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who

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required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1617]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each gGroup who ~~developed their respective outcome measure of survival~~survived to 36 weeks PMA without BPD~~ at 36 weeks~~. ~~Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering~~ Analysis of this and all other categorical outcomes was performed using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. Continuous outcomes were analyzed using mixed effects linear models. In analysis of all outcomes, adjustment was performed as pre-specified for gestational age stratum, center and familial clustering. A two-sided P value of less than 0.05 was considered statistically significant.

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An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. {Lan-DeMets spending functions with Pocock or {O'Brien-Fleming} boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

Comment [MG2]: Also chest compressions and/or epinephrine in the DR, pulmonary hemorrhage, and nasal breakdown requiring the discontinuation of nasal prongs.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through ~~to Mar 1~~Feb ~~2009 .~~2009. Enrollment ~~The trial~~ was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual~~conceptional~~ age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.83~~2~~, 1.01~~0~~, p=0.0~~60~~72) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,~~,~~ 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03~~3~~, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.9~~4~~3, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, ~~nor any differences in~~ length of stay, ~~or~~ days of oxygen for survivors, or discharge on oxygen~~.~~ (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.01~~9~~). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. Nearly a~~A~~ll infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p<0=.00~~1~~05). ~~The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non-~~

Comment [MG3]: Not in table

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~~significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)~~

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants and Hispanic infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.033. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.023 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata. The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[19] or need for surgical intervention for ROP was non-significantly reduced in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75, 95% CI 0.54, 1.05).

Comment [MG7]: Race is not in tab le

Comment [MG8]: Not in table

Comment [MG9]: These numbers were reported above but are for the 24-25 week GA stratum

26-27 weeks Gestation

There was no significant difference in mortality for the CPAP vs Surfactant groups, 110% vs 101%. The CPAP infants required fewer days of oxygen, ~~40.6~~44.0 vs ~~47.1~~49.5, p=0.035~~1~~, and lesser days of mechanical ventilation, ~~11.3~~13.7 vs ~~14.9~~16.7, p=0.085~~1~~, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p=<0.008~~1~~.

Comment [MG10]: Non-significant

Discussion:

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The SUPPORT Ttrial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant ~~given within an hour of life~~ in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention~~other outcome~~ that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[20] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[21]

Our trial~~study~~ differs from the recently reported COIN trial[15~~15~~] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who ~~all~~ were to received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that intent to treat with early CPAP and protocol driven limited ventilator strategy ~~when compared~~compared to ~~with~~ surfactant given within 1 hour of birth was associated with a non-significant decrease in death ~~or survival with~~by 36 weeks PMA or

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BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted ~~a very~~ significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along ~~with reductions~~with reductions in BPD, ~~ROP, significantly,~~ significantly decreased durations of mechanical ventilation ~~and oxygen~~, a decreased need for intubation and exposure to post natal steroids in the overall CPAP ~~group without~~group without any increase in adverse neonatal ~~outcomes represents~~outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks~~, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium~~. We did not find an increase in airleaks in the first 14 days of life with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial~~study~~ was a factorial design with each infant randomly ~~receiving 2~~receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of

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survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with ~~the use of~~randomization to surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment~~ed~~ with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death ~~or survival with~~by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks ~~PCA~~ PMA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=6634)	Surfactant (N=6532)	Unadjusted P-value
GA (weeks)	24-25	43% (285/663)43% (285/664)	43% (280/653)43% (280/652)	0.96860.9932
	26-27	57% (378/663)57% (379/664)	57% (373/653)57% (372/652)	
Male		52% (342/663)52% (342/664)	57% (370/653)57% (370/652)	0.06460.0646
Race/ethnicity	Non-Hispanic Black	38% (254/663)38% (255/664)	36% (235/653)36% (234/652)	0.368103681
	Non-Hispanic White	38% (250/663)38% (250/664)	42% (271/653)42% (271/652)	
	Hispanic	21% (138/663)21% (138/664)	19% (121/653)19% (121/652)	
	Other/unknown	3% (21/663)3% (21/664)	4% (26/653)4% (26/652)	
Birth weight (grams)	Mean±StdDev (n=1316)	834.6 ± 188.2834.8 ± 188.2	825.5 ± 198.1825.6 ± 198.3	0.39620.3855
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.126.2 ± 1.1	26.2 ± 1.126.2 ± 1.1	0.64630.6420
Antenatal steroids (any)		97% (642/663)97% (643/664)	96% (623/652)96% (622/651)	0.22480.2206
Antenatal steroids (full course)		74% (486/660)74% (486/661)	70% (453/649)70% (452/648)	0.12320.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)0% (1/663)	1% (5/653)1% (6/652)	0.09780.0978

Table 2. Delivery Room Interventions

Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370

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~~Characteristic~~	~~CPAP (N=663)~~	~~Surfactant (N=653)~~	~~Unadjusted P-value~~
~~Apgar at 5 minutes <3~~	~~4% (26/663)~~	~~5% (32/653)~~	~~0.3870~~
~~PPV in the DR (SUPP03)~~	~~66% (435/662)~~	~~93% (606/652)~~	~~<0.0001*~~
~~Intubated in DR (SUPP03)~~	~~34% (227/660)~~	~~93% (609/652)~~	~~<0.0001*~~
~~DR intubation for resuscitation~~	~~33% (216/660)~~	~~27% (176/652)~~	~~0.0271*~~
~~Surfactant in DR (SUPP03)~~	~~14% (93/660)~~	~~51% (335/652)~~	~~<0.0001*~~
~~Surfactant in DR or NICU (SUPP03, SUPP04)~~	~~67% (443/660)~~	~~99% (646/653)~~	~~<0.0001*~~
~~Chest compressions in DR (SUPP03)~~	~~5% (36/660)~~	~~6% (40/653)~~	~~0.6026~~
~~Epinephrine in DR (SUPP03)~~	~~2% (13/660)~~	~~4% (27/653)~~	~~0.0225*~~

~~Characteristic~~	~~CPAP (N=663)~~	~~Surfactant (N=653)~~	~~Relative Risk for CPAP vs. Surfactant (95% CI)~~	~~Unadjusted P-value~~
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81% (538/663)	22% (146/653)	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	33% (215/660)	27% (176/652)	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 3. Other Outcomes

Characteristic	CPAP (N=6634)	Surfactant (N=6532)	Relative Risk for CPAP vs. Surfactant (95% CI)	~~Unadjusted~~ Adjusted P-value
Death in the first week	6% (40/663)~~6%~~	6% (39/653)~~6% (39/651)~~	0.99 (0.64, 1.53)	0.9575~~0.9630~~

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	~~(40/664)~~			
Death at any time while hospitalized	16% (109/663)~~16% (109/664)~~	20% (128/653)~~20% (127/651)~~	0.84 (0.67, 1.05)	0.12590.1~~440~~
Total LOS any hospital (survivors only) Mean±StdErr (N=1075)	104.8 ± 2.0~~100.4 ± 42.9~~	106.2 ± 2.0~~101.4 ± 41.6~~		0.59670.7~~047~~
Days on supplemental oxygen (survivors to discharge, transfer or 120 days only) Mean±StdErr (N=1098)	62.2 ± 1.6~~55.0 ± 37.8~~	65.3 ± 1.6~~58.5 ± 37.6~~		0.12150.1~~229~~
Days on mechanical vent (HFV & CV) (survivors to discharge, transfer or 120 days only) Mean±StdErr (N=1098)	24.8 ± 1.0~~20.0 ± 23.9~~	27.7 ± 1.1~~23.2 ± 26.2~~		0.02870.0~~331~~
Discharge on oxygen	22% (122/550)~~22% (122/550)~~	24% (124/519)~~24% (124/519)~~	0.98 (0.8, 1.2)	0.82020.5~~067~~
Alive and off MV (HFV/CV) at 7 days	55% (362/655)~~55% (362/655)~~	49% (318/652)~~49% (318/652)~~	1.14 (1.03, 1.25)	0.01110.0~~188~~
Any air leak in first 14 days	7% (45/663)~~7% (45/663)~~	7% (48/653)~~7% (48/653)~~	0.89 (0.6, 1.32)	0.55530.6~~901~~
Medical or surgical NEC	13% (83/654)~~13% (83/654)~~	10% (63/636)~~10% (63/636)~~	1.25 (0.92, 1.71)	0.14690.1~~144~~
PDA requiring surgery	11% (73/653)~~11% (73/653)~~	11% (68/636)~~11% (68/636)~~	1 (0.73, 1.36)	0.99370.7~~793~~
IVH grade 3-4	14% (92/642)~~14% (92/642)~~	11% (72/628)~~11% (72/628)~~	1.26 (0.94, 1.68)	0.12230.1~~279~~
Postnatal steroids for BPD	7% (47/649)~~7% (47/650)~~	13% (83/631)~~13% (83/629)~~	0.57 (0.41, 0.78)	0.00050.0~~005~~

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	~~Unadjusted~~ Adjusted P-value
Death in the first week	9% (25/285)~~9% (25/285)~~	10% (29/280)~~10% (29/280)~~	0.86 (0.51, 1.45)	0.56460.~~5217~~
Death at any time while hospitalized	24% (68/285)~~24%~~	32% (90/280)~~32%~~	0.74 (0.57, 0.98)	0.03350.~~0264*~~

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	~~(68/285)~~	~~(90/279)~~		
Total LOS any hospital (survivors only) Mean±StdErr (N=407)	122.0 ± 2.9~~120.7 ± 47.9~~	119.0 ± 3.1~~119.2 ± 40.5~~		0.46900~~.7394~~
Days on supplemental oxygen (survivors to discharge, transfer or 120 days only) Mean±StdErr (N=421)	80.8 ± 2.3~~76.9 ± 34.3~~	80.3 ± 2.4~~78.1 ± 33.5~~		0.86480~~.7269~~
Days on mechanical vent (HFV & CV) (survivors to discharge, transfer or 120 days only) Mean±StdErr (N=421)	35.8 ± 1.5~~33.1 ± 27.3~~	38.7 ± 1.6~~37.5 ± 29.0~~		0.17220~~.1138~~
Discharge on oxygen	32% (69/214)~~32% (69/214)~~	31% (59/188)~~31% (59/188)~~	1.08 (0.82, 1.41)	0.58780~~.8535~~
Alive and off MV (HFV/CV) at 7 days	34% (97/283)~~34% (97/283)~~	26% (74/280)~~26% (74/280)~~	1.29 (1, 1.66)	0.04860~~.0429*~~
Any air leak in first 14 days	8% (23/285)~~8% (23/285)~~	10% (27/280)~~10% (27/280)~~	0.79 (0.47, 1.35)	0.39540~~.5105~~
Medical or surgical NEC	15% (42/279)~~15% (42/279)~~	13% (35/268)~~13% (35/268)~~	1.13 (0.74, 1.71)	0.57980~~.5026~~
PDA requiring surgery	16% (46/279)~~16% (46/279)~~	17% (46/268)~~17% (46/268)~~	0.9 (0.62, 1.3)	0.58190~~.8325~~
IVH grade 3-4	20% (54/273)~~20% (54/273)~~	17% (45/265)~~17% (45/265)~~	1.17 (0.82, 1.68)	0.38970~~.4022~~
Postnatal steroids for BPD	13% (36/276)~~13% (36/276)~~	20% (54/264)~~20% (54/264)~~	0.66 (0.46, 0.94)	0.02260~~.0209*~~

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Table 2. Other outcomes for CPAP vs. Surfactant

Characteristic	Category	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week		6% (40/663)	6% (39/653)	0.99 (0.64, 1.53)	0.9575
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1075)	104.8 ± 2.0	106.2 ± 2.0		0.5967
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1079)	101.4 ± 2.0	101.5 ± 2.0		0.9444
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	62.2 ± 1.6	65.3 ± 1.6		0.1215
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	24.8 ± 1.0	27.7 ± 1.1		0.0287
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=1082)	57.5 ± 0.9	58.8 ± 0.9		0.2240
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	17.3 ± 0.6	16.8 ± 0.6		0.4713
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	3.4 ± 0.3	3.7 ± 0.3		0.4552
Discharge on oxygen (NG03 or NG05)		22% (122/550)	24% (124/519)	0.98 (0.8, 1.2)	0.8202
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		55% (362/655)	49% (318/652)	1.14 (1.03, 1.25)	0.0111
Pneumothorax (NG03 or SUPP08)		8% (54/663)	6% (36/653)	1.46 (0.96, 2.21)	0.0786
Any air leak in first 14 days (SUPP08)		7% (45/663)	7% (48/653)	0.89 (0.6, 1.32)	0.5553
Medical or surgical NEC (NG03)		13% (83/654)	10% (63/636)	1.25 (0.92, 1.71)	0.1469
PDA requiring surgery (NG03)		11% (73/653)	11% (68/636)	1 (0.73, 1.36)	0.9937
IVH grade 3-4 (NG03)		14% (92/642)	11% (72/628)	1.26 (0.94, 1.68)	0.1223
PVL (NG03 or MRI01)		4% (28/643)	4% (26/629)	1.09 (0.63, 1.88)	0.7538
Death or PVL (NG03 or MRI01)		20% (134/663)	23% (147/653)	0.9 (0.74, 1.11)	0.3185
Postnatal steroids for BPD (NG03)		7% (47/649)	13% (83/631)	0.57 (0.41, 0.78)	0.0005
Postnatal steroids after DOL 21 (SUPP09)		17% (114/659)	23% (149/652)	0.75 (0.61, 0.92)	0.0069
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	0.37 (0.34, 0.42)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		77% (508/661)	100% (649/652)	0.77 (0.74, 0.8)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		83% (551/663)	100% (651/653)	0.83 (0.8, 0.86)	<0.0001

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Table 2: Other outcomes for CPAP vs. Surfactant Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs Surfactant (95% CI)	Adjusted P-value
Death in the first week		9% (25/285)	10% (29/280)	0.86 (0.51, 1.45)	0.5646
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=405)	122.0 ± 2.9	119.0 ± 3.1		0.4690
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=407)	118.0 ± 2.9	116.0 ± 3.1		0.6331
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	80.8 ± 2.3	80.3 ± 2.4		0.8648
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	35.8 ± 1.5	38.7 ± 1.6		0.1722
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=421)	68.7 ± 1.3	68.6 ± 1.3		0.9669
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	19.5 ± 0.9	18.0 ± 1.0		0.2355
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=421)	4.9 ± 0.4	5.1 ± 0.4		0.8283
Discharge on oxygen (NG03 or NG05)		32% (69/214)	31% (59/188)	1.08 (0.82, 1.41)	0.5878
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		34% (97/283)	26% (74/280)	1.29 (1, 1.66)	0.0486
Pneumothorax (NG03 or SUPP08)		10% (29/285)	8% (21/280)	1.29 (0.74, 2.26)	0.3626
Any air leak in first 14 days (SUPP08)		8% (23/285)	10% (27/280)	0.79 (0.47, 1.35)	0.3954
Medical or surgical NEC (NG03)		15% (42/279)	13% (35/268)	1.13 (0.74, 1.71)	0.5798
PDA requiring surgery (NG03)		16% (46/279)	17% (46/268)	0.9 (0.62, 1.3)	0.5819
IVH grade 3-4 (NG03)		20% (54/273)	17% (45/265)	1.17 (0.82, 1.68)	0.3897
PVL (NG03 or MRI01)		6% (17/273)	5% (14/265)	1.23 (0.6, 2.52)	0.5684
Death or PVL (NG03 or MRI01)		29% (83/285)	36% (100/280)	0.82 (0.65, 1.05)	0.1180
Postnatal steroids for BPD (NG03)		13% (36/276)	20% (54/264)	0.66 (0.46, 0.94)	0.0226
Postnatal steroids after DOL 21 (SUPP09)		28% (78/282)	34% (94/279)	0.8 (0.63, 1.02)	0.0697
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	0.54 (0.48, 0.61)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		88% (250/285)	99% (278/280)	0.88 (0.84, 0.92)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		94% (267/285)	100% (279/280)	0.94 (0.91, 0.97)	0.0003

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Table 2. Other outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death in the first week		4% (15/378)	3% (10/373)	1.36 (0.61, 3.02)	0.4561
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=670)	88.3 ± 2.4	92.3 ± 2.4		0.2147
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=672)	85.1 ± 2.4	86.5 ± 2.4		0.6422
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	44.0 ± 1.9	49.5 ± 1.9		0.0349
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	13.7 ± 1.3	16.7 ± 1.3		0.0848
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean±StdErr (N=661)	46.5 ± 1.1	48.8 ± 1.1		0.1113
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	15.3 ± 0.8	15.3 ± 0.8		0.9790
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=677)	1.9 ± 0.3	2.3 ± 0.3		0.4346
Discharge on oxygen (NG03 or NG05)		16% (53/336)	20% (65/331)	0.88 (0.64, 1.2)	0.4118
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		71% (265/372)	66% (244/372)	1.09 (0.98, 1.2)	0.1016
Pneumothorax (NG03 or SUPP08)		7% (25/378)	4% (15/373)	1.69 (0.9, 3.17)	0.1021
Any air leak in first 14 days (SUPP08)		6% (22/378)	6% (21/373)	1.01 (0.57, 1.81)	0.9652
Medical or surgical NEC (NG03)		11% (41/375)	8% (28/368)	1.42 (0.9, 2.25)	0.1353
PDA requiring surgery (NG03)		7% (27/374)	6% (22/368)	1.22 (0.7, 2.14)	0.4875
IVH grade 3-4 (NG03)		10% (38/369)	7% (27/363)	1.41 (0.86, 2.3)	0.1732
PVL (NG03 or MRI01)		3% (11/370)	3% (12/364)	0.92 (0.4, 2.12)	0.8434
Death or PVL (NG03 or MRI01)		13% (51/378)	13% (47/373)	1.07 (0.74, 1.55)	0.7304
Postnatal steroids for BPD (NG03)		3% (11/373)	8% (29/367)	0.4 (0.2, 0.78)	0.0076
Postnatal steroids after DOL 21 (SUPP09)		10% (36/377)	15% (55/373)	0.67 (0.45, 0.99)	0.0433
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	0.24 (0.2, 0.29)	<0.0001
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		69% (258/376)	100% (371/372)	0.68 (0.64, 0.74)	<0.0001
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		75% (284/378)	100% (372/373)	0.75 (0.7, 0.79)	<0.0001

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Table 3. BPD outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	16% (109/663)	20% (128/653)	0.84 (0.67, 1.05)	0.1259
Death by 36 weeks PMA	14% (94/663)	17% (114/653)	0.81 (0.63, 1.03)	0.0890
BPD (physiologic definition)	39% (223/569)	41% (219/539)	0.99 (0.87, 1.14)	0.9172
BPD (physiologic definition) or death by 36 weeks PMA	48% (317/663)	51% (333/653)	0.95 (0.85, 1.05)	0.3039
BPD (supplemental O2)	40% (229/569)	44% (239/539)	0.94 (0.82, 1.06)	0.3178
BPD (supplemental O2) or death by 36 weeks PMA	49% (323/663)	54% (353/653)	0.91 (0.83, 1.01)	0.0719
ROP	14% (70/517)	14% (68/480)	0.95 (0.7, 1.28)	0.7406
ROP or death	28% (176/620)	32% (193/601)	0.87 (0.74, 1.03)	0.0971

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3 BPD outcomes for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	24% (68/285)	32% (90/280)	0.74 (0.57, 0.98)	0.0335
Death by 36 weeks PMA	20% (57/285)	29% (82/280)	0.68 (0.5, 0.92)	0.0125
BPD (physiologic definition)	55% (125/228)	55% (108/198)	1.06 (0.91, 1.25)	0.4570
BPD (physiologic definition) or death by 36 weeks PMA	64% (182/285)	68% (190/280)	0.96 (0.85, 1.07)	0.4470
BPD (supplemental O2)	54% (122/228)	54% (106/198)	1.05 (0.9, 1.23)	0.5329
BPD (supplemental O2) or death by 36 weeks PMA	63% (179/285)	67% (188/280)	0.95 (0.84, 1.06)	0.3578
ROP	23% (47/202)	31% (55/175)	0.75 (0.54, 1.05)	0.0994
ROP or death	42% (112/266)	55% (144/261)	0.74 (0.62, 0.89)	0.0015

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3. BPD outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Death at any time while hospitalized	11% (41/378)	10% (38/373)	1.06 (0.7, 1.6)	0.7966
Death by 36 weeks PMA	10% (37/378)	9% (32/373)	1.12 (0.72, 1.75)	0.6055
BPD (physiologic definition)	29% (98/341)	33% (111/341)	0.92 (0.74, 1.15)	0.4621
BPD (physiologic definition) or death by 36 weeks PMA	36% (135/378)	38% (143/373)	0.94 (0.78, 1.13)	0.4828
BPD (supplemental O2)	31% (107/341)	39% (133/341)	0.84 (0.69, 1.02)	0.0812
BPD (supplemental O2) or death by 36 weeks PMA	38% (144/378)	44% (165/373)	0.87 (0.74, 1.03)	0.1163
ROP	7% (23/315)	4% (13/305)	1.86 (0.94, 3.67)	0.0728
ROP or death	18% (64/354)	14% (49/340)	1.25 (0.88, 1.77)	0.2153

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 1. Patient Description for CPAP vs. Surfactant

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43% (285/663)	43% (280/653)	0.9686
	26-27	57% (378/663)	57% (373/653)	
Male		52% (342/663)	57% (370/653)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (254/663)	36% (235/653)	0.3681
	Non-Hispanic White	38% (250/663)	42% (271/653)	
	Hispanic	21% (138/663)	19% (121/653)	
	Other/unknown	3% (21/663)	4% (26/653)	
Birth weight (grams)	Mean (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Antenatal steroids (any)		97% (642/663)	96% (623/652)	0.2248
Antenatal steroids (full course)		74% (486/660)	70% (453/649)	0.1232
Death in the DR (SUPP03/SUPP04)		0% (1/663)	1% (5/653)	0.0978

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Table 1b. DR outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)	Adjusted P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.92 (0.76, 1.11)	0.3835
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.82 (0.5, 1.34)	0.4281
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	0.71 (0.67, 0.75)	<0.0001
CPAP in the DR (SUPP03)	81% (538/663)	22% (146/653)	3.66 (3.16, 4.25)	<0.0001
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	33% (215/660)	27% (176/652)	1.21 (1.02, 1.43)	0.0243
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	0.28 (0.23, 0.34)	<0.0001
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	0.67 (0.64, 0.71)	<0.0001
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.86 (0.57, 1.31)	0.4807
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.48 (0.25, 0.91)	0.0240

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (106/280)	0.0495*
	Non-Hispanic White	32% (92/285)	43% (120/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.3 ± 139.5	0.0713
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1149
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (SUPP03)		73% (207/284)	95% (267/280)	<0.0001*
CPAP in the DR (SUPP03)		72% (205/285)	22% (62/280)	<0.0001*
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
DR intubation for resuscitation		48% (137/284)	31% (87/280)	<0.0001*
Surfactant in DR (SUPP03)		21% (60/284)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		77% (220/284)	99% (276/280)	<0.0001*
Chest compressions in DR (SUPP03)		9% (27/285)	8% (23/280)	0.5982
Epinephrine in DR (SUPP03)		4% (10/285)	5% (15/280)	0.2854
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (SUPP03/SUPP04)		0% (1/285)	1% (4/280)	0.1715

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Male		52% (195/378)	56% (208/373)	0.2511
Race/ethnicity	Non-Hispanic Black	35% (132/378)	35% (129/373)	0.8733
	Non-Hispanic White	42% (158/378)	40% (151/373)	
	Hispanic	20% (75/378)	20% (76/373)	
	Other/unknown	3% (13/378)	5% (17/373)	
Birth weight (grams)	Mean (n=751)	922.2 ± 180.5	921.0 ± 181.4	0.9325
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.9676
Apgar at 1 minute <3		18% (66/377)	22% (83/373)	0.1034
Apgar at 5 minutes <3		2% (7/378)	3% (13/373)	0.1645
PPV in the DR (SUPP03)		60% (228/378)	91% (339/372)	<0.0001*
CPAP in the DR (SUPP03)		88% (333/378)	23% (84/373)	<0.0001*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
DR intubation for resuscitation		21% (78/376)	24% (89/372)	0.2964
Surfactant in DR (SUPP03)		9% (33/376)	50% (186/372)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		59% (223/376)	99% (370/373)	<0.0001*
Chest compressions in DR (SUPP03)		2% (9/375)	5% (17/373)	0.1072
Epinephrine in DR (SUPP03)		1% (3/375)	3% (12/373)	0.0184*
Antenatal steroids (any)		96% (363/378)	94% (352/373)	0.2865
Antenatal steroids (full course)		70% (262/375)	68% (251/371)	0.5146
Death in the DR (SUPP03/SUPP04)		0% (0/378)	0% (1/373)	0.3138

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; wrich@ucsd.edu
Subject: RE: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 3:39:30 PM
Attachments: Graphs for Survival Analysis in Oximetry Arm.doc
Oxygen Saturation Target.11.6.09.MASTER_MG.doc

Attached is the Oxygen Saturation paper with my edits and comments. I have updated all numbers and p-values. I have added to the methods section on statistical analysis, and I have added the survival analysis. Instead of using Kaplan-Meier analysis I have used Cox regression in order to adjust for stratification and clustering as in the other analyses. The results were similar, although the difference in the survival curves was significant (p=0.045) after adjustment and non-signficant in the KM analysis without the adjustments. See attached for the two survival curves for comparison.

I will also update all numbers in the CPAP paper and send that out as well.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, November 08, 2009 3:06 PM
To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz, Marie; 'wrich@ucsd.edu'
Cc: 'MSumner@peds.uab.edu'
Subject: Re: Oxygen Saturation paper for your comments.

I think neil and wally on behalf of the support subcommittee of the nichd nrn is fine. If space permits, marie and wade can be added. Limitation in author number was instituted because the authors were taking up to 25 percent of alloted space.
I need the abstract in the next day or so for nichd clearance.
Thanks

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>
Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 13:27:55 2009
Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf
On both Abstracts I would like at least you and me as authors and then whatever follows

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I will put Finer, Carlo, you can do the flip side
I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

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Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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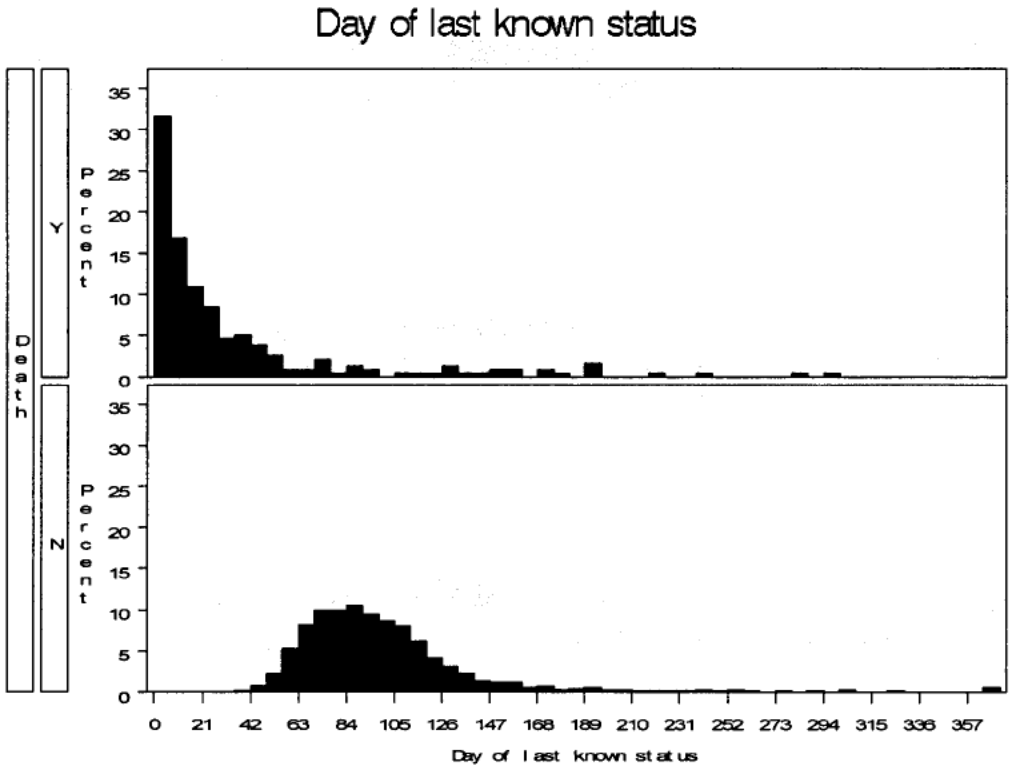
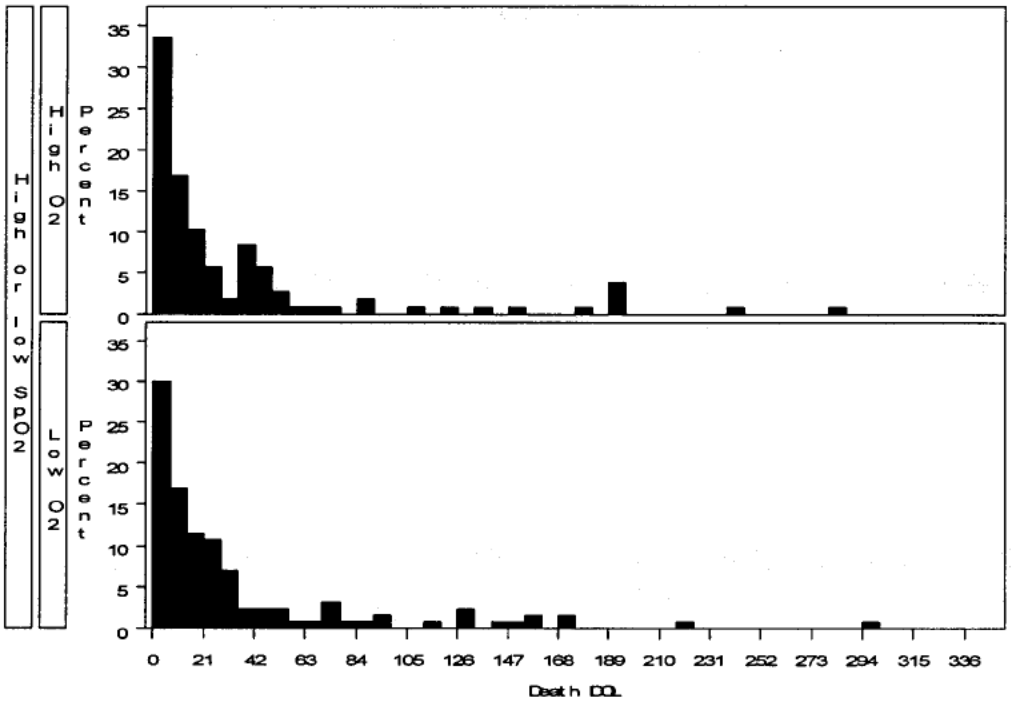
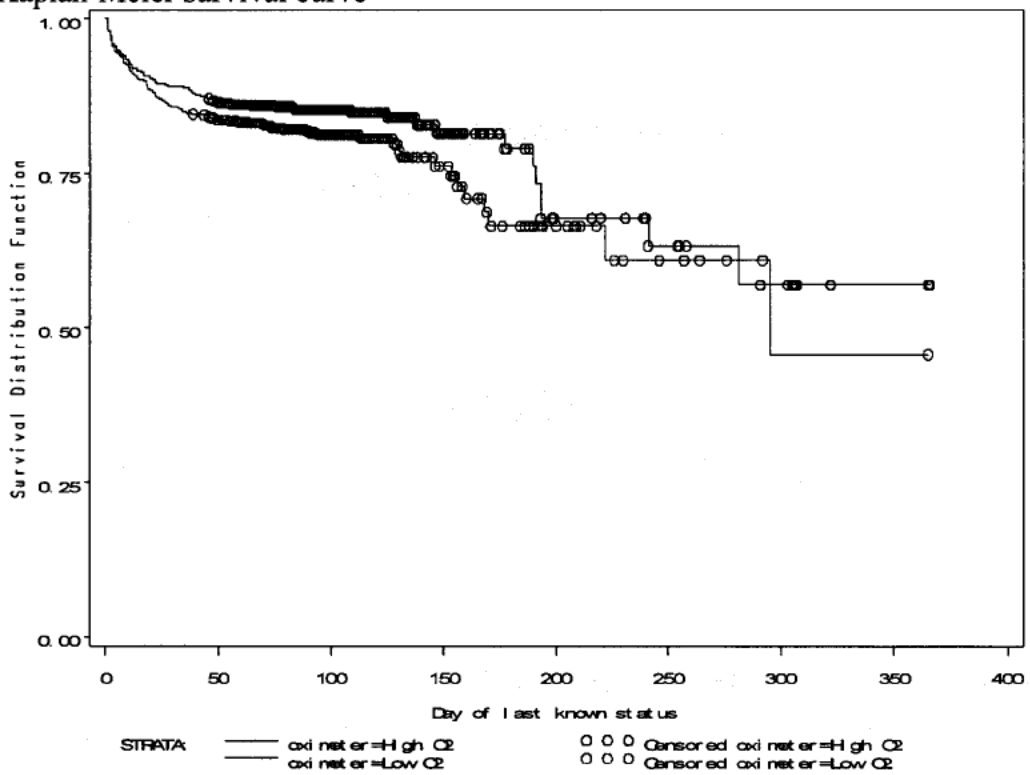
Histograms and KM Graph for Survival Analysis in Oximetry Arm
11/08/09



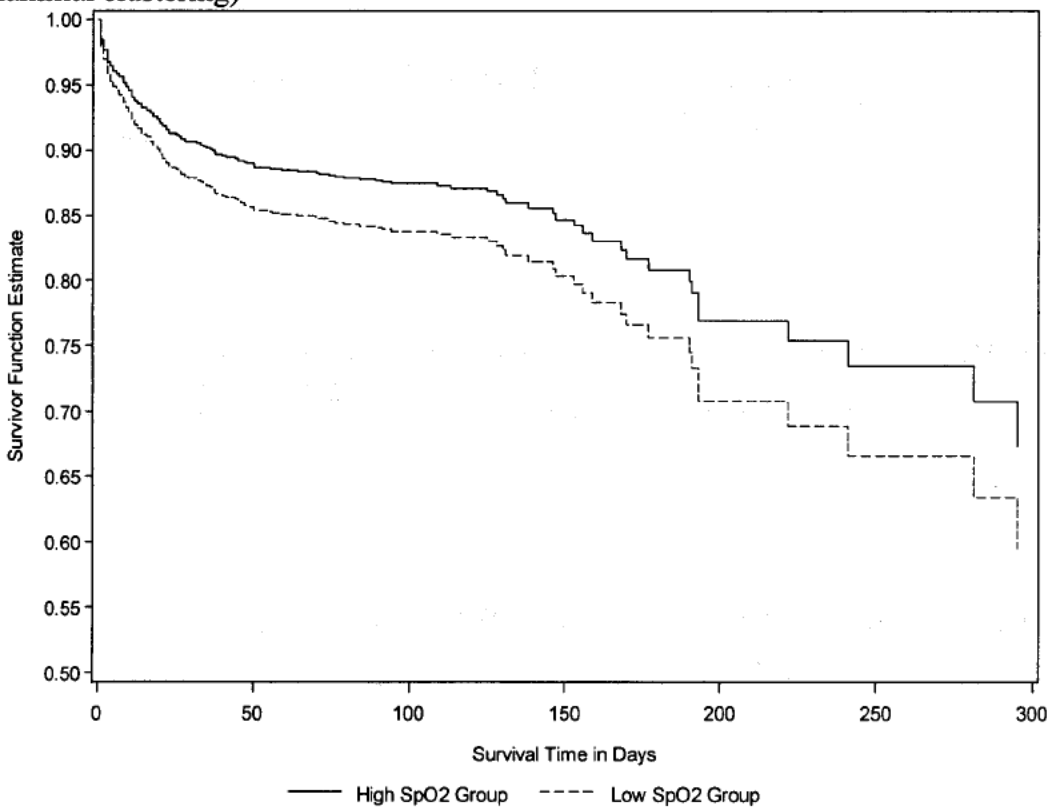


This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Kaplan-Meier survival curve



Cox regression survival curve (adjusted for stratification by center and GA group and for familial clustering)



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11/06/09
7.0

Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

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Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

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Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Word count:

Abstract: 212

Manuscript: 2449

Running head: Oxygen saturation and outcomes of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; adjusted p-value = ~~—~~). ~~–~~0.205). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; adjusted p-value = 0.~~—~~) .041) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; adjusted p-value= ~~—~~).0.0001).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

Comment [MG1]: 3 of the randomized infants were actually 28 0/7 weeks GA

Comment [MG2]: Do we need to be specific and say threshold or ROP surgery? Not all infants who had surgery for ROP also had an exam with threshold in our data.

Comment [MG3]: These numbers include 13 infants who died (6 who had ROP and 7 who did not). Do you want me to remove them so it's strictly ROP among survivors?

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and those known to have major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than ~~85~~84% or higher than ~~95~~96%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

Comment [MG4]: The offset was 3% in the target ranges, but at points above and below the target ranges where the display values were transitioning back to "actual" values the offset was not necessarily 3%

Comment [MG5]: A display value of 84 in the high target group corresponds to actual values of 84-87. Below 84 the display values correspond to actual values in both treatment groups.

Comment [MG6]: A display value of 96 in the low target group corresponds to actual values of 93-96. Above 96 the display values correspond to actual values in both treatment groups.

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy or surgery or Avastin treatment for ROP. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present ~~up to 55 weeks post-menstrual age~~:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of categorical outcomes for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks (RR) comparing incidence rates for infants in each treatment arm who developed the

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primary outcome. Continuous outcomes were analyzed using mixed effects linear models. Survival analysis using Cox regression produced a hazard ratio (HR) for comparing mortality in the low and high oxygen saturation groups. ~~The model produces relative risk estimates~~ GEE, mixed effect and survival models were adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided adjusted p-value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and

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Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ~~——~~247 infants to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

Comment [MG7]: Also need for chest compressions and/or epinephrine in the DR, pulmonary hemorrhage, and nasal breakdown requiring the discontinuation of nasal prongs.

RESULTS

1316 infants were enrolled between ~~January~~ February ~~2004~~ 2005 and ~~March~~ February 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; ~~p=~~adjusted p-value

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0.~~____~~-.205; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.041). Comparable results were observed for both gestational age strata. ~~Kaplan Meier Analysis indicated~~ Cox regression analysis indicated that there was a significantly higher hazard of death in the lower oxygen saturation group (HR 1.32; CI 1.01, 1.72; p= 0.045) (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy or surgical intervention for ROP was decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0.~~_____~~).-.0001). Oxygen use at 36 weeks PMA was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks PMA and the composite outcome of bronchopulmonary dysplasia/death by 36 weeks PMA did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

Comment [MG8]: These numbers include 13 infants who died (6 who had ROP and 7 who did not). Do you want me to remove them so it's strictly ROP among survivors?

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

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The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy or the need for surgical intervention for ROP, it also increased the risk for mortality.

This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.87% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for

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saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy or surgical intervention/death but it increased mortality and decreased threshold retinopathy or surgical intervention. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85

Comment [MG9]: Is this still true after some trials have switched to the new oximeter algorithm?

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to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 6545)	Higher Saturation Group (N = 6621)
Birthweight – g (m±SD)	8365±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	341/654 (52)~~342/655 (52)~~	371/662 (56)~~370/661 (56)~~
Race or ethnic group – no. (%)		
White (non-Hispanic)	242/654 (37)~~242/655 (37)~~	279/662 (42)~~279/661 (42)~~
Black (non-Hispanic)	257/654 (39)~~258/655 (39)~~	232/662 (35)~~231/661 (35)~~
Hispanic	132/654 (20)~~132/655 (20)~~	127/662 (19)~~127/661 (19)~~
Other/unknown	23/654 (4)~~23/655 (4)~~	24/662 (4)~~24/661 (4)~~
Antenatal corticosteriods (any) – no. (%)	633/654 (97)~~634/655 (97)~~	632/661 (96)~~631/660 (96)~~
Antenatal corticosteroids (full course) – no. (%)	477/651 (73)~~478/652 (73)~~	462/658 (70)~~460/657 (70)~~
5-min Apgar score < 3 – no. (%)	34/654 (5)~~34/655 (5)~~	24/662 (4)~~24/661 (4)~~
Surfactant in the DR or NICU – no. (%)	531/653 (81)~~532/654 (81)~~	558/660 (85)~~557/659 (85)~~

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Table 2. Major Outcomes

~~Predischarge o~~Outcome – no./total no. (%)	Lower Saturation Group N=654 n/N (%)	Higher Saturation Group N=662 n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy or surgical intervention/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy or surgical intervention	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/662~~1~~ (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/662~~1~~ (8)	1.20 ~~(1.2~~ (0.84, 1.~~7~~0)
Death by 36 weeks PMA	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203~~2~~/540 (38~~7~~)	265/568 (47)	0.82~~1~~ (0.72~~1~~, 0.93~~2~~)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	317~~6~~/654 (48)	359/662 (54)	0.91 (0.83~~2~~, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage $\geq$ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage $\geq$ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)

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Medical treatment for patent ductus arteriosus	219/634 (35~~6~~)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (10~~4~~)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	43~~2~~/662 (6)	1.12 (0.74, 1.68)
Any air ~~leaks~~ leaks in the first 14 days – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

~~Characteristic~~Outcome	Lower Saturation Group	Higher Saturation Group	Adjusted P-value[1]
Length of stay any hospital, (days) m+~~SD~~SE*	104.5 ± 2.0~~99±39~~	106.4 ± 2.0~~102±43~~	0.45~~0.17~~
Length of stay NRN hospital, (days) m+~~SD~~SE*	99.8 ± 2.0~~95±41~~	103.0 ± 2.0~~99±44~~	0.22~~0.08~~
Duration of mechanical ventilation, (days) m+~~SD~~SE†	25.5 ± 1.1~~21±25~~	26.9 ± 1.0~~23±25~~	0.30~~0.21~~
Duration of oxygen supplementation, (days) m+~~SD~~SE†	59.8 ± 1.6~~52±38~~	67.4 ± 1.5~~61±37~~	0.0002~~<0.001~~
Continuous positive airway pressure, (days) m+SE†~~SD~~	17.1 ± 0.6~~16±14~~	17.0 ± 0.6~~16±14~~	0.94~~0.95~~
Nasal synchronized intermittent mandatory ventilation, (days) m+SE†~~SD~~	3.3 ± 0.3~~3±7~~	3.8 ± 0.3~~4±7~~	0.14~~0.06~~
Alive off mechanical ventilation by day 14, (days) – no. (%)~~m+SD~~	332/644 (52)~~331/643 (51)~~	326/655 (50)~~322/649 (50)~~	0.86~~0.50~~
Alive off mechanical ventilation by day 7, (days) – no. (%)~~m+SD~~	351/648 (54)	329/659 (50)	0.27

* Among survivors to discharge, transfer or one year; maximum value is 366 days

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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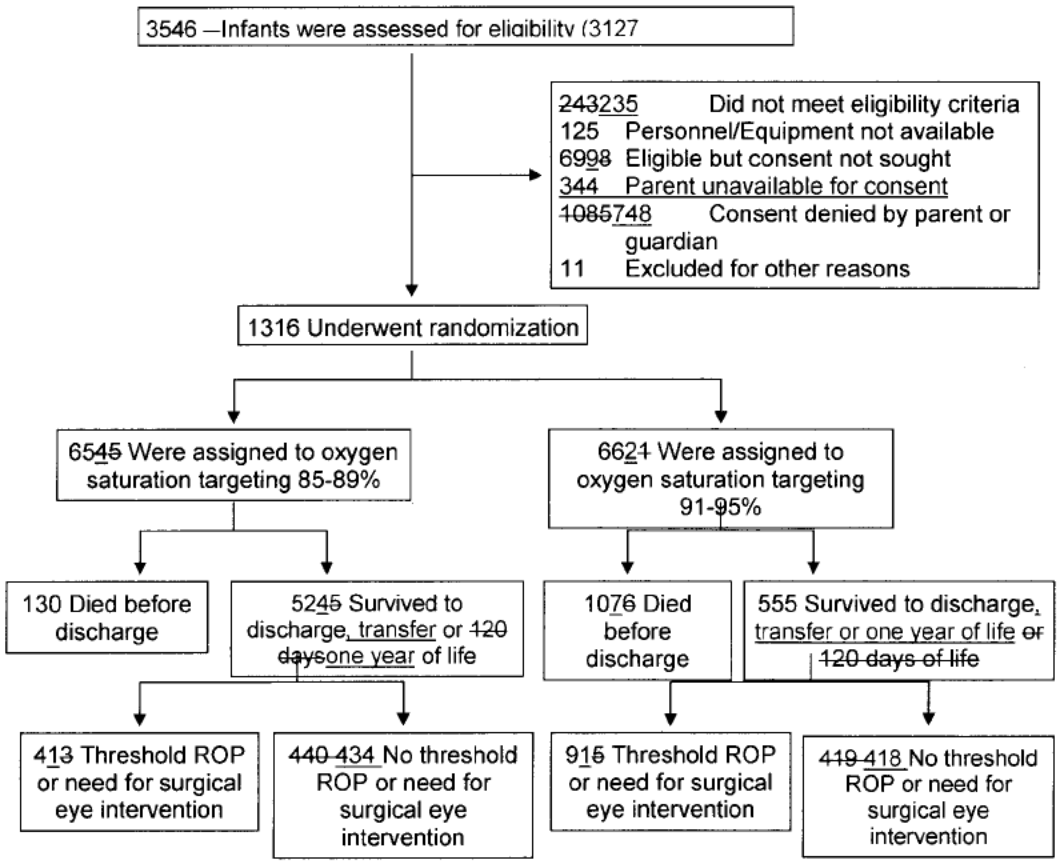
Figure 1

Comment [MG10]: We might need additional boxes at the bottom of the figure for those who survived but are missing the final ROP outcome: 49 in the low group and 46 in the high group.



* Excludes mothers who were screened who did not subsequently deliver a GDB (or SUPPORT) baby

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Figure 2 ~~Kaplan Meier plot~~Survivor Curve for ~~m~~Mortality ~~(from Marie)~~

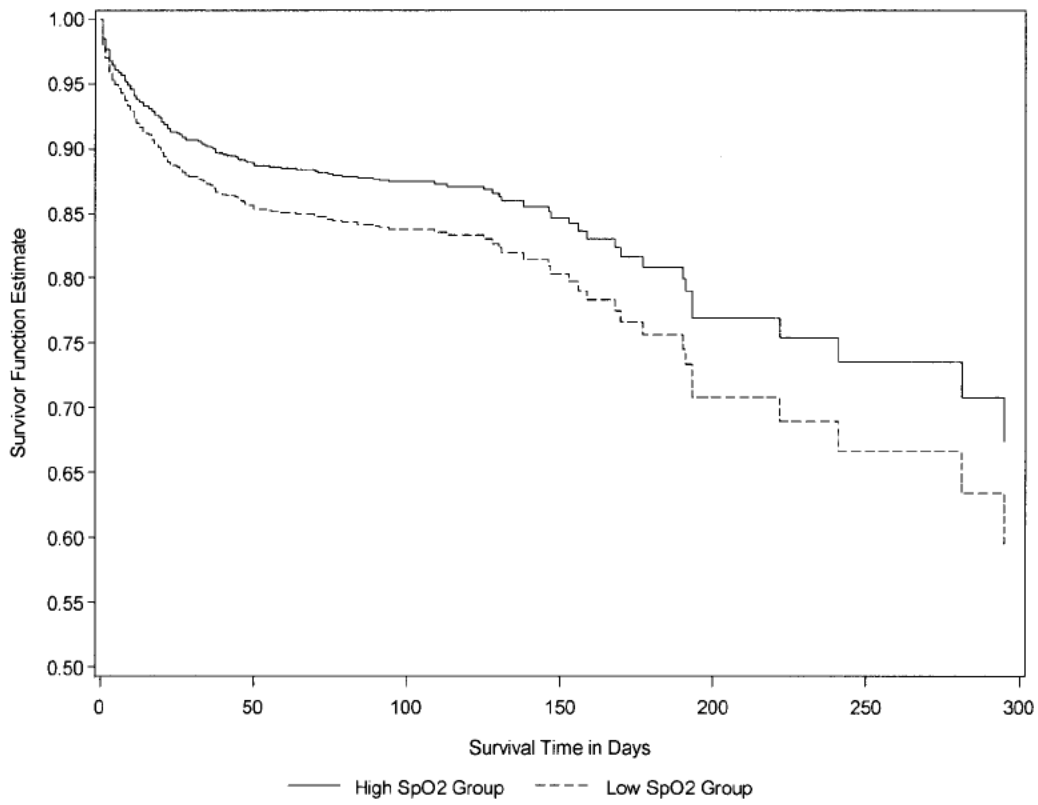

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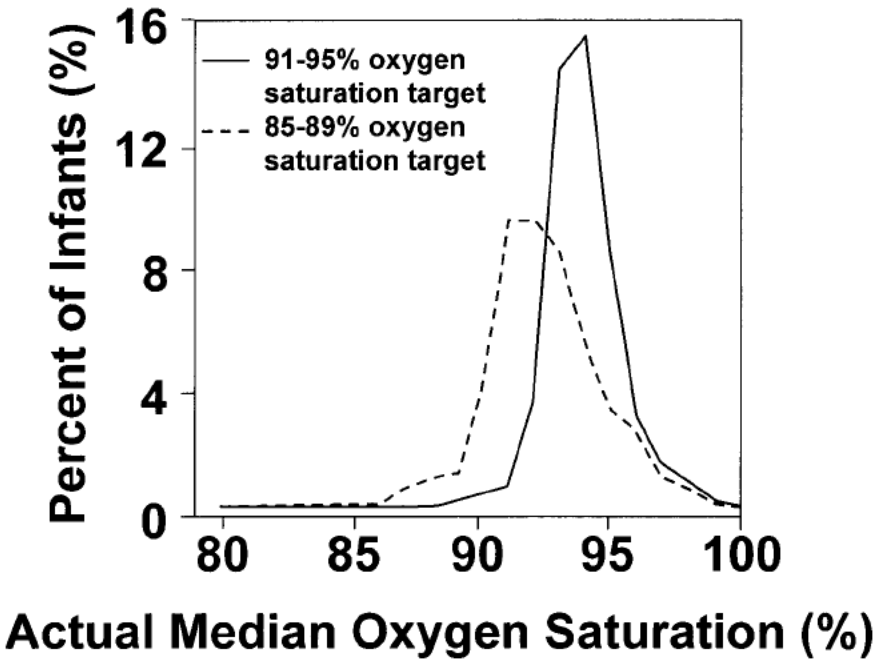
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Page 23: [1] Formatted	Marie Gantz	11/8/2009 12:03:00 PM

Font: (Default) Times New Roman, 10 pt

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From: Laptook, Abbot
To: Wally Carlo, M.D.; Michele Walsh; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 3:12:46 PM

Wally
This manuscript reads very well and appears to be pretty bullet proof. I like Ed Bell's suggestions. I don't see much to comment on except for a few minor points:
1) Abstract/results: if the word allotment allows it would be good to indicate how similar the groups were in demographic characteristics.
2) Results/table 3: No results are listed for alive off mechanical ventilation by day 7.

Abstract: also looks great. Only comment would be in the methods to indicate that the target saturations were for when infants were in oxygen.

Great job!! Tx, AL

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 5:33 PM
To: Michele Walsh; Laptook, Abbot; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wally Carlo, M.D.
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Wally

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Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 11:25:57 PM
Attachments: First Author.doc

Hi Neil:

Here are a few suggestions on the abstract.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
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Birmingham, AL 35233-7335
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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, November 08, 2009 9:48 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
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Please review
Neil

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Subject: RE: Oxygen Saturation paper for your comments.

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If you can fit more authors, it is fine

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Cc: Marsha Sumner <MSumner@peds.uab.edu>
Sent: Sun Nov 08 17:18:45 2009
Subject: RE: Oxygen Saturation paper for your comments.

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Rose:

OK?

Wally

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Cc: Marsha Sumner
Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
I am working on the abstract for CPAP and Surf
On both Abstracts I would like at least you and me as authors and then

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whatever follows
I will put Finer, Carlo, you can do the flip side
I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade
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Subject: FW: Oxygen Saturation paper for your comments.

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The paper and the PAS draft are enclosed.

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From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
Cc: Wally Carlo, M.D.
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Edwin M. Dixon Professor of Pediatrics

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First Author: Neil N Finer

File Number: 751689

Presenting Author: Neil N Finer

Responsible Author: Neil N Finer

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Neiul n Finer MD

Formatted: Italian (Italy)

Department/Institution/Address: Department of Pediatrics, Division of Neonatology,, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812 **E-mail:** nfiner@ucsd.edu

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Responsible Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Responsible Author E-mail: nfiner@ucsd.edu

Responsible Author Declaration:
As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, 402 Dickinson St., MPF 1-140 Department of Pediatrics, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Presenter E-mail: nfiner@ucsd.edu

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Is Presenting Author a Trainee? No, Not a Trainee

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Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

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Awards Applied for:

Consider for PAS Travel Grant Award: No

Sponsoring Member for PAS Abstracts
Sponsored by: Neil Norman Finer,
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring societies:
Society for Pediatric Research
Academic Pediatric Association

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants –The SUPPORT Trial

Neil N Finer, MD, Waldemar A Carlo, MD and the Neonatal Research Network of the NICHD.
[1]Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, San Diego, Ca, United States and [2]Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States.

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Objective: The SUPPORT Trial was designed to compare early CPAP with early surfactant in ELBW infants.

Design/Methods: The SUPPORT Trial~~study~~ was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while receiving supplemental oxygen

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was non-significantly reduced at 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.83, 1.01, p=0.07 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). Overall, more CPAP infants were alive and off mechanical ventilation by day 7, (55% vs 49%, p=0.01~~1~~) and fewer required intubation (83% vs 100%, P<0.0001) or post natal steroids for BPD (7% vs 13%, p<.0.0005). There was no difference in the occurrence of air leaks in the first 14 days, severe intraventricular~~t~~ hemorr~~h~~hage, medical or surgical necrotizing enterocolitis, or patent ductus arteriosus requiring surgery.

Conclusions: Compared with randomization to surfactant within 1 hour of birth, ~~ELBW~~ infants between 24 and 27 6/7ths weeks gestation at birth assigned to treatment with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death by 36 weeks PMA or BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse

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neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Finer, Neil
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Rich, Wade
Cc: Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 10:47:43 PM
Attachments: PAS CPAP vs Surf SUPPORT Nov 08 09.dot

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Sent: Sunday, November 08, 2009 2:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; mgantz@rti.org; Rich, Wade
Subject: RE: Oxygen Saturation paper for your comments.

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University of Alabama at Birmingham
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Subject: RE: Oxygen Saturation paper for your comments.

Hi Wally
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On both Abstracts I would like at least you and me as authors and then whatever follows
I will put Finer, Carlo, you can do the flip side
I don't know how many authors the NRN requires on abstracts but we will have 2 anyway- if we can do more I would put Wade, Rose and Marie.
Let me know
Neil

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First Author: Neil N Finer

File Number: 751689

Presenting Author: Neil N Finer

Responsible Author: Neil N Finer

Subspecialty: Neonatology - General

Theme: Neonatal Medicine: Clinical Trials

2010 PAS Annual Meeting

Contact Person: Neiul n Finer MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology,, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812 **E-mail:** nfiner@ucsd.edu

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Responsible Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, 402 Dickinson St., MPF 1-140, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Responsible Author E-mail: nfiner@ucsd.edu

Responsible Author Declaration:
As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD

Department/Institution/Address: Department of Pediatrics, Division of Neonatology, 402 Dickinson St., MPF 1-140Deoartment of Pediatri, San Diego, Ca, 92103-8774, United States

Phone: 619 543 3285 **Fax:** 619 543 3812

Presenter E-mail: nfiner@ucsd.edu

The presenting author is member of these Alliance Societies:

Is Presenting Author a Trainee? No, Not a Trainee

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Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Research type: Clinical

Presentation conflict on: N/A

APA Special Interest Groups, Committees or Regions:

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Awards Applied for:

Consider for PAS Travel Grant Award: No

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Sponsored by: Neil Norman Finer,
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring societies:
Society for Pediatric Research
Academic Pediatric Association

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants –The SUPPORT Trial

Neil N Finer, MD, Waldemar A Carlo, MD and the Neonatal Research Network of the NICHD.
[1]Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center, San Diego, Ca, United States and [2]Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States.

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From: Finer, Neil
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts
Date: Sunday, November 08, 2009 10:07:24 PM

Thanks Marie
We will now finalize the paper and Abstract
When you can, please lets get the Consent paper ready
Thanks
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Sunday, November 08, 2009 6:36 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts

Neil,

Here is your paper with updated numbers and my edits, as well as the three source tables I have produced before, now with adjusted p-values and RRs where appropriate.

Will there also be a table showing the primary outcomes? Right now the variables covered in the text and tables don't seem to match completely.

I saw the messages about adding a decimal to the percentages, but not before I had run this version. I will re-run the CPAP and SpO2 paper tables tomorrow with the decimal.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 04, 2009 1:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: Re: manuscripts

Hi Rose
Here is the SUPPORT CPAP Surf paper with Tables for circulation
Neil
On 11/4/09 9:33 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

Hi,
Can you send me the updated versions of the manuscripts for distribution

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to the SC members and co-authors by Monday?? Have you received input from the subcommittee members?

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Wally Carlo, M.D.
To: Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts
Date: Sunday, November 08, 2009 9:39:26 PM

Marie:

Thanks!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Sunday, November 08, 2009 8:36 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: manuscripts

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Marie

Marie Gantz, Ph.D.
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RTI International
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828-254-6255

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Sent: Wednesday, November 04, 2009 1:02 PM

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Cc: Das, Abhik; Gantz, Marie
Subject: Re: manuscripts

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<higginsr@mail.nih.gov> wrote:

Hi,
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Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Finer, Neil
To: Wally Carlo, M.D.
Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: Re: Oxygen Saturation paper for your comments.
Date: Sunday, November 08, 2009 9:06:12 PM

I agree with using decimals
Neil

Sent from my iPhone

On Nov 8, 2009, at 2:38 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> ALL:
>
> I have a suggestion. Because our sample size is much larger that 100
> per
> group and closer to 1000 (as we all know), we should consider using a
> decimal point in the percentages. The reason is that rounding to full
> percentages obscures important information. For example, a close to 3%
> difference in mortality between the CPAP vs int/surf group is
> rounded to
> 4% but is not statistically significant. The difference of 4% in the
> mort of the sat groups is statistically sig. The other reason for
> adding
> a decimal is for more precise estimate of the NNT.
>
> Let me know what you think so we do it the same way on both papers.
>
> Wally
>
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266(b) (6)
>
> -----Original Message-----
> From: Gantz, Marie [mailto:mgantz@rti.org]
> Sent: Sunday, November 08, 2009 2:39 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo,
> M.D.; Das, Abhik; wrich@ucsd.edu
> Subject: RE: Oxygen Saturation paper for your comments.
>
> Attached is the Oxygen Saturation paper with my edits and comments. I
> have updated all numbers and p-values. I have added to the methods

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> section on statistical analysis, and I have added the survival
> analysis.
> Instead of using Kaplan-Meier analysis I have used Cox regression in
> order to adjust for stratification and clustering as in the other
> analyses. The results were similar, although the difference in the
> survival curves was significant (p=0.045) after adjustment and
> non-signficant in the KM analysis without the adjustments. See
> attached
> for the two survival curves for comparison.
>
> I will also update all numbers in the CPAP paper and send that out as
> well.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Sunday, November 08, 2009 3:06 PM
> To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz,
> Marie;
> 'wrich@ucsd.edu'
> Cc: 'MSumner@peds.uab.edu'
> Subject: Re: Oxygen Saturation paper for your comments.
>
> I think neil and wally on behalf of the support subcommittee of the
> nichd nrn is fine. If space permits, marie and wade can be added.
> Limitation in author number was instituted because the authors were
> taking up to 25 percent of alloted space.
> I need the abstract in the next day or so for nichd clearance.
> Thanks
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary
> (NIH/NICHD) [E]; adas@rti.org <adas@rti.org>; Gantz, Marie
> <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>
> Cc: Marsha Sumner <MSumner@peds.uab.edu>
> Sent: Sun Nov 08 13:27:55 2009
> Subject: RE: Oxygen Saturation paper for your comments.
>
> Hi Wally
> I am working on the abstract for CPAP and Surf
> On both Abstracts I would like at least you and me as authors and then
> whatever follows
> I will put Finer, Carlo, you can do the flip side
> I don't know how many authors the NRN requires on abstracts but we
> will
> have 2 anyway- if we can do more I would put Wade, Rose and Marie.
> Let me know
> Neil
>

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> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 3:46 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie;
> Finer, Neil; Rich, Wade
> Cc: Marsha Sumner
> Subject: FW: Oxygen Saturation paper for your comments.
>
> I am sorry that my assistant did not send the email to the whole
> subcommittee (see below) .
>
> The paper and the PAS draft are enclosed.
>
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266(b) (6)
>
> -----Original Message-----
> From: Wally Carlo, M.D.
> Sent: Friday, November 06, 2009 4:33 PM
> To: Michele Walsh; ALaptook@wihri.org; 'Bradley.yoder@hsc.utah.edu';
> 'roger.faix@hsc.utah.edu'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'
> Cc: Wally Carlo, M.D.
> Subject: Oxygen Saturation paper for your comments.
>
>
>
> Dear SUPPORT Subcommittee members:
>
> Enclosed is a draft of the oxygen saturation paper for your
> comments. I
> need everyone's comments before we can submit to the Publications
> Subcommittee and the whole Steering Committee which gets it at the
> same
> time. I am also enclosing the first draft of the PAS abstract which
> is
> currently slightly above the word limit.
>
> Wally
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> Phone: 205 934 4680

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>

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From: Vineet Bhandari
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Sunday, November 08, 2009 2:47:02 PM
Attachments: Oxygen Saturation Target.11.6.09.MASTER VB edit Nov 8 2009.DOC
Importance: High

Hello, Wally,

Please find attached your manuscript with some minor edits, mostly in the 1st paragraph on page 11 (introduction). I thought the sentence was too long and convoluted. In addition:

1. While the number of infants enrolled are the same, the dates of enrollment are different in Neil's ("Feb 2005 to Mar 2009") vs. your paper ("January 2004 and March 2009").

2. Besides some missing "p-values" and "numbers" in the text, I thought Table 1 should have p-values.

3. Table 3 is missing data in the last row.

4. I did not get Figure 2. I assume it is OK.

5. Finally, I agree with Ed Bell's comment that the "number needed to prevent threshold ROP" and the "number needed to harm/cause death" should be included in the "discussion" of the mansucript.

Hope this helps.

Best wishes.
Vineet.

At 07:40 AM 11/7/2009, you wrote:

> The O2 sat paper went out without figures due to some computer glitch. Here is a copy with the 2 figures.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> ---
>
> **From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, November 06, 2009 3:42 PM

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To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:
November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675(b) (6) with passcode(b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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11/06/09
7.0

Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [2]University of California at San Diego, San Diego, CA; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center,

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Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]Univresity of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

Waldemar A. Carlo, M.D.

University of Alabama at Birmingham

525 New Hillman Building

619 South 20th Street

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Phone: (205) 934 4680

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD.PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

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Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these multiple studies suggest that maintenance of oxygenation at lower ranges may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including death.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

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Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2 factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

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Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

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An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively.

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Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary

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dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There have not been other randomized controlled trials of different oxygen targeting starting soon after birth to

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reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

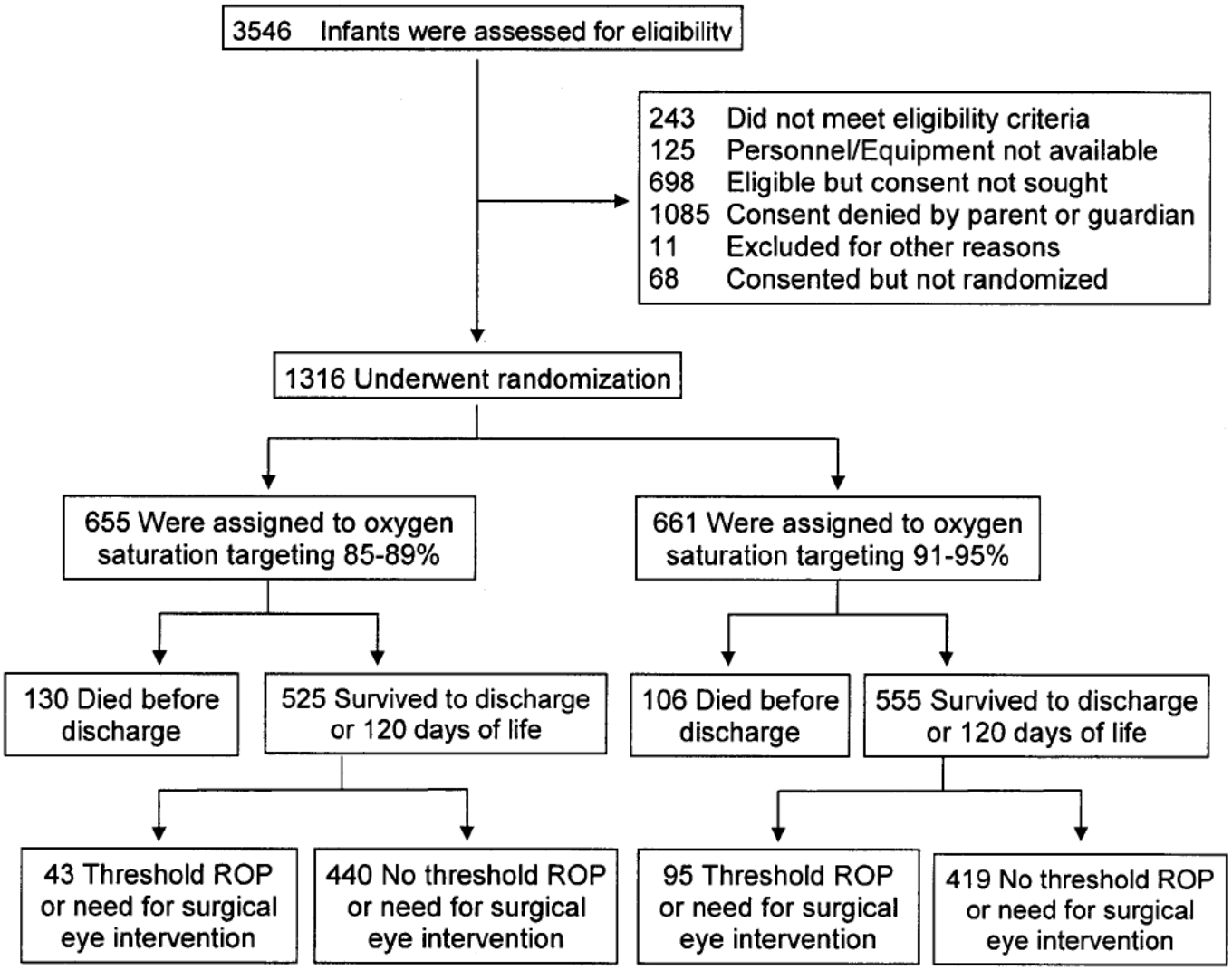

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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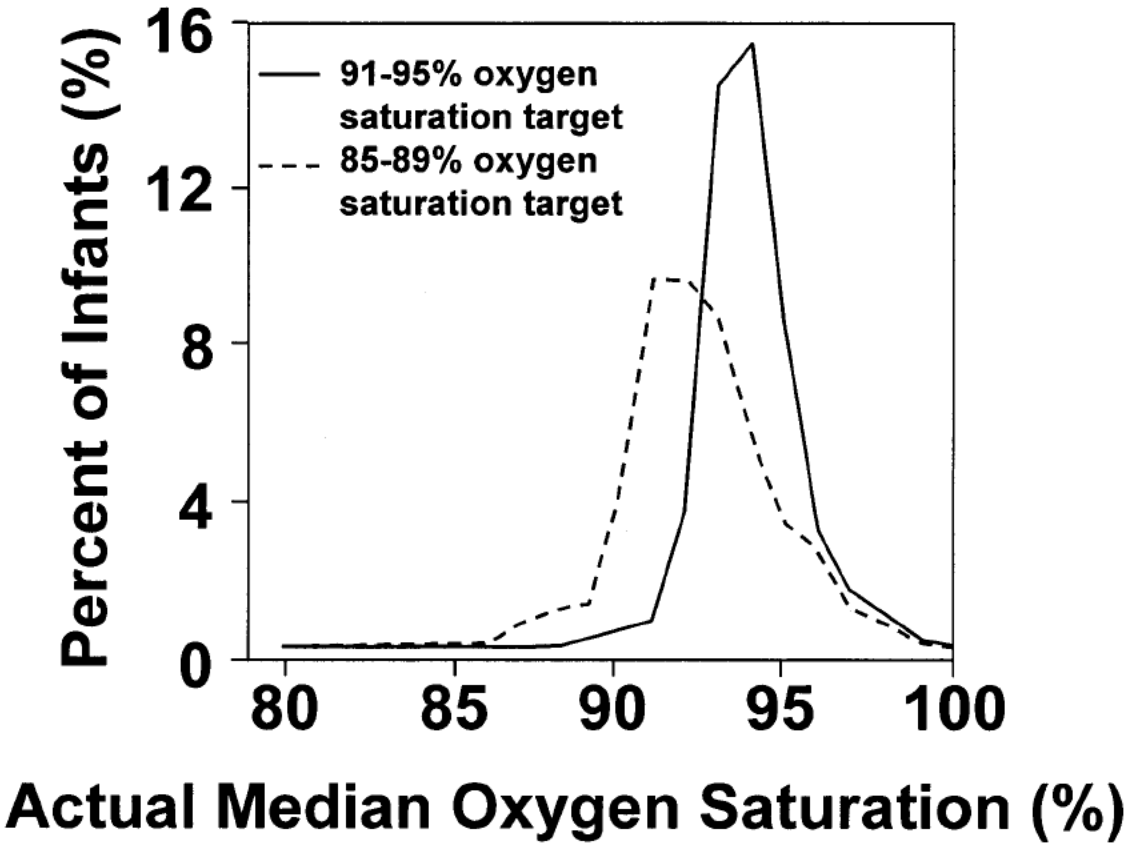
Figure 3



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The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From:	Vineet Bhandari
To:	Finer, Neil
Cc:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date:	Sunday, November 08, 2009 2:28:42 PM
Attachments:	SUPPORT CPAP vs Surf Nov 3 09 doc for circ (2) VB edit Nov 8 2009.docx SUPPORT Manuscript - Network Version Word Nov 6 09 VB edit Nov 8 2009.doc SUPPORT CPAP vs Surfactant Tables Word Nov 3 09 VB edit Nov 8 2009.doc
Importance:	High

Hello, Neil,

The version Rose sent out had the correct author list on the face page. The text was similar in both versions. My (mostly minor) edits are attached for both versions, and the tables. You should be able to pick them up with "track changes".

1. I have highlighted the 2 correct names of the authors on the face page, for your convenience.

2. Please let me know if any questions or clarifications.

Thanks.
Vineet.

At 12:26 PM 11/7/2009, you wrote:
>Here are the Tables as Word 2004 docs
>Neil
>
>
>On 11/7/09 9:09 AM, "Neil Finer" <nfiner@ucsd.edu> wrote:
>
>Hi Again
>The previous version was unreadable by most Sorry for that
>Here is a Word doc that I hope all can read
>Neil
>
>
>On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:
>
>Hi Rose and Everyone
>I cleaned up the previous version and accepted
>all Abhiks edits and made a few more corrections.
>Please keep confidential
>Look forward to your comments
>Neil
>
>
>On 11/6/09 1:41 PM, "Higgins, Rosemary
>(NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>
>Hi,

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>Attached are the two papers in draft form for
>the SUPPORT Primary outcomes. As noted, there
>is an increase in death in the lower saturation
>group (20%) versus the higher saturation group (16%).
>
>This information is confidential and a plan is
>in place for DSMC communication with ongoing
>trials of oxygen saturation. If you are
>contacted by any investigators from other trials
>or elsewhere, do not share this information. If necessary, refer them to me.
>
>The plan for submission is as follows:
>
>
>November 16 4 PM call for Steering committee
>and authors to discuss papers. In the meantime,
>feel free to send comments to Neil and Wally. The call in number is:
>866-675-(b) (6) with passcode 5(b) (6)
>
>If you are not going to be on the call, send
>comments in advance or designate someone to serve in your absence.
>
>Immediately following the call, the manuscripts
>will be finalized for NICHD clearance and for
>submission to the New England Journal of Medicine.
>
>Thanks in advance to everyone for all their hard work!!!
>Rose
>
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Word count:

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Manuscript: 3080

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven minimal ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 ~~min~~ minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<0.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, but~~and~~ was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation. Overall surfactant has not been reported to significantly reduce bronchopulmonary dysplasia (BPD), but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (-9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[444], and a reduction in death or the need for oxygen at

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28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol-directed ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven

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minimal ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, -and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator- or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant wa~~s~~is urgently required.

NICU management: Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While

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intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within one hour of intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, ~~An~~ FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20- bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial, intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was

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known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. (Lan-DeMets spending functions with Pocock and (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through to Mar ~~1~~ 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or

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race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post ~~conceptional~~ menstrual age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 9~~0~~5% CI 0.82, 1.00, p=0.060) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata~~,~~, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP

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infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75 (0.54, 1.05)

Strata Results: 24 – 25 weeks Gestation (post hoc analysis)

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[15,15,15] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven minimal ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven minimal ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that early CPAP and protocol driven mimimal ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven minimal ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD (p<.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, but was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation. Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[4], and a reduction in death or the need for oxygen at 28

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days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited

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ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP, both at a recommended 5 cm H_2O, was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant was urgently required.

NICU management: Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While

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intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within one hour of intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, FiO2 $\leq$ 35 with a SpO2 $\geq$88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial, intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was

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known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through to Mar 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or

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race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 95% CI 0.82, 1.00, $p=0.060$) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, $p=0.03$, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP

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infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[15] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that early CPAP and protocol driven limited ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3681
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0978

Table 2. Delivery Room interventions

Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	<0.0001*
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation	33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.0225*

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9630
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	100.4 ± 42.9	101.4 ± 41.6	0.7047
Days on supplemental oxygen (survivors only)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors only)	20.0 ± 23.9	23.2 ± 26.2	0.0331
Discharge on oxygen	22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days	55% (362/655)	49% (318/652)	0.0188
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC	13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery	11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4	14% (92/642)	11% (72/628)	0.1279
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0005

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/280)	0.5217
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.7 ± 47.9	119.2 ± 40.5	0.7394
Days on supplemental oxygen (survivors only)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors only)	33.1 ± 27.3	37.5 ± 29.0	0.1138
Discharge on oxygen	32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days	34% (97/283)	26% (74/280)	0.0429*
Any air leak in first 14 days	8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC	15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery	16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4	20% (54/273)	17% (45/265)	0.4022
Postnatal steroids for BPD	13% (36/276)	20% (54/264)	0.0209*

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From: Finer, Neil
To: Laptook, Abbot; Wally Carlo, M.D.; Michele Walsh; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CPAP vs intubation
Date: Sunday, November 08, 2009 12:58:49 PM

Thanks Abbot
I will fix
The sentence in the paragraph near the end is missing the word overall - Deaths in the lower strata and overall decreases in the other outcomes
As always you can be counted on for a thorough and very useful review. I will incorporate your suggestions
Be well
Neil

-----Original Message-----
From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Sunday, November 08, 2009 8:35 AM
To: Wally Carlo, M.D.; Michele Walsh; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu; Finer, Neil
Cc: HigginsR@mail.nih.gov
Subject: RE: CPAP vs intubation

Neil
Nice paper; you have summarized a tremendous amount of data in very succinct, clear manner. I have a few relatively minor comments:
1) Abstract, last sentence: considering changing the words "such infants" to ELBW infants or state the GA studied
2) Introduction, second paragraph: The first sentence states that BPD is reduced with surfactant but the 3rd sentence states that is is not reduced. A little confusing of the point you are trying to make.
3) Introduction, last paragraph: The statement of the hypothesis would be better placed here rather than in the methods. Especially for casual readers who may only read the abstract/intro/discussion it should be clear what we were testing.
4) Methods/CPAP arm/NICU management: For intubation criteria you have "an arterial PaCO2>65 torr documented on a single blood gas within one hour of intubation". Maybe modify the end of that statement to "...within one hour prior to intubation..."
5) Methods/Surfactant arm: First statement is that all infants were intubated with 1 hours of life and received surfactant. The protocol states that all infants were intubated in the DR and received surfactant in the DR or within one hour of life.
6) Methods/Safety outcomes: Were any DR outcomes monitored and should they be listed.
7) Results/first paragraph: The last sentence deals with DR (epi and deaths) and would be better grouped with the second paragraph. Also why not move death in the DR to table 2 which is focused on DR since table 1 is really demographics.
8) Results/compliance: A reviewer may want some information of compliance with the protocol since in table 2 93% of surfactant infants were intubated in the DR but the protocol states they all should be intubated in the DR.
9) Results/3rd paragraph: The statement "There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen..." may be clearer if you state "...occurrence of BPD based on the use of supplemental oxygen..."
10) Severe IVH: do you ever define this? Maybe insert a definition in the table legend.
11) Discussion/3rd paragraph: The statement "We believe that this lower incidence of death in these infants along with reduction in BPD, ROP, significantly decreased durations of ventilation and oxygen...". The only differences that I see are the deaths, off ventilation at day 7 and use of steroids for this strata.
Tx, hope this helps. AL

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

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Sent: Friday, November 06, 2009 5:33 PM
To: Michele Walsh; Laptook, Abbot; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

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From: Fanaroff, Avroy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 5:35:47 PM

I now have Neal's manuscript and tables
My other E mails are aaf2@case.edu or (b) (6)
University Hospitals has been hit with a major virus and half the computers have been down for a week
They have totally blocked the Internet
all we get is E mail
cannot even use the library
as indicated will try and get the review done rapidly
Results are interesting to say the least
Regards
Av

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sat 11/7/2009 7:08 AM
To: Fanaroff, Avroy
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Av
The emails are bouncing - do you have an alternate email?? Aol, gmail, yahoo etc?

From: Fanaroff, Avroy <Avroy.Fanaroff@UHhospitals.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Nov 07 00:13:50 2009
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Rose
I will try
I am heading to Florida on the 11th
By the way I am unable to open the figures and tables - please resend
The ROP/Mortality findings are intriguuing
almost like the 50's when restricted oxygen reduced retinopathy but increased mortality
The follow up will be even more rvealing, especially if the low sat group have more problems - or did the low sats weed out the weak?
Be well
Av
PS Note still burning the candle at both ends

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 11/6/2009 4:45 PM
To: Ed Donovan; Fanaroff, Avroy; Stevenson David (E-mail); jon.e.tyson@uth.tmc.edu
Cc: Wally; nfiner@ucsd.edu
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,
You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits.

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If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

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301-496-3790 (FAX)
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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; "Nancy Newman"; "Susie Buchter"; "Brenda Morris"; "Laroia, Nirupama"; Sood, Beena; Shahnaz Duara; "Michael O`Shea"; Anthony Piazza; vineet.bhandari@yale.edu; "Vivek.Narendran@cchmc.org"; Dale Phelps; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); Av Fanaroff; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo; cotte010@mc.duke.edu; Dennis Wallace; Edward Bell; Ed Donovan; Ehrenkranz@Yale. Edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh-Sukys; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Ken Poole; Roger Faix; Duke. Edu>;; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Jon Tyson; VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; Cunningham, Meg; Carolyn Petrie
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 12:27:04 PM
Attachments: Tables Word Nov 3 09.doc

Here are the Tables as Word 2004 docs
Neil

On 11/7/09 9:09 AM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Again
The previous version was unreadable by most – Sorry for that
Here is a Word doc that I hope all can read
Neil

On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

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866-675-(b) (6) with passcode (b) (6)

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Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	03681
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0978

Table 2. Delivery Room interventions

Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	<0.0001*
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation	33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.0225*

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9630
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	100.4 ± 42.9	101.4 ± 41.6	0.7047
Days on supplemental oxygen (survivors only)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors only)	20.0 ± 23.9	23.2 ± 26.2	0.0331
Discharge on oxygen	22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days	55% (362/655)	49% (318/652)	0.0188
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC	13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery	11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4	14% (92/642)	11% (72/628)	0.1279
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0005

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/280)	0.5217
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.7 ± 47.9	119.2 ± 40.5	0.7394
Days on supplemental oxygen (survivors only)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors only)	33.1 ± 27.3	37.5 ± 29.0	0.1138
Discharge on oxygen	32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days	34% (97/283)	26% (74/280)	0.0429*
Any air leak in first 14 days	8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC	15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery	16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4	20% (54/273)	17% (45/265)	0.4022
Postnatal steroids for BPD	13% (36/276)	20% (54/264)	0.0209*

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From: Phelps, Dale
To: Gantz, Marie; Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting
Date: Saturday, November 07, 2009 12:25:54 PM

I have some concerns about ROP primary outcomes as late as after 55 weeks. We were pushing things a bit to take it even to 55 weeks. It would depend on the sequence of examination findings.

If an infants lat examination prior to the "determining" examination were at 37 weeks PMA as he was going home, and the next examination was at 58 weeks PMA (over 5 months later), there would not be a way to know what had happened in-between. Could have met criteria, or not.

Let us look carefully at that distribution of PMAs.
We don't want to publish methods/definitions that will not be credible to the ROP community.

Dale

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, November 06, 2009 3:13 PM
To: Wally Carlo, M.D.; Phelps, Dale; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

I'll have to look at the distribution of PMAs when final ROP status is obtained.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 6:12 PM
To: Gantz, Marie; Phelps, Dale; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

I will have to change this in the methods.

How late are the ROP outcomes followed?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

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Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, November 06, 2009 4:51 PM
To: Wally Carlo, M.D.; Phelps, Dale; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

The ROP outcome is not just up to 55 weeks. Sometimes infants have reached final ROP status after that point.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 5:50 PM
To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

I got it. It is not predischarge only. I will fix the heading. In the text, it is stated that it the ROP outcome is to 55 weeks.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
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Cell: 205 266(b) (6)

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, November 06, 2009 4:38 PM
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

Not really. Many, if not most, infants were discharged long before 55 weeks PMA. (table 3 shows medians of 99 or 102 days (=~14 weeks). If

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the infants were median 26 weeks, they were discharged to home at median 40 weeks. No where near 55 weeks.

You have listed ROP in the table of outcomes under the subheading:
"Predischarge Outcome"

That is my issue.
Dale

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 2:23 PM
To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

Dale:

We included the ROP outcomes up to 55 weeks PMA. Does that clarify your concern?
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, November 06, 2009 3:35 PM
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting

Wally,
The first thing I note is that the ROP is probably reported incorrectly.

To the best of my understanding, the data provided to you by RTI is Threshhold ROP which occurred at any time. Some of these were after discharge.

Dale

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 12:47 PM
To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT Subcommittee Meeting

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Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; "Nancy Newman"; "Susie Buchter"; "Brenda Morris"; "Laroia, Nirupama"; Sood, Beena; Shahnaz Duara; "Michael O`Shea"; Anthony Piazza; vineet.bhandari@yale.edu; "Vivek.Narendran@cchmc.org"; Dale Phelps; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); Av Fanaroff; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo; cotte010@mc.duke.edu; Dennis Wallace; Edward Bell; Ed Donovan; Ehrenkranz@Yale. Edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh-Sukys; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Ken Poole; Roger Faix; Duke. Edu>:; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Jon Tyson; VanMeurs, Krisa
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Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 12:09:50 PM
Attachments: SUPPORT Manuscript - Network Version Word Nov 6 09.doc

---

Hi Again
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Here is a Word doc that I hope all can read
Neil

On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
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November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode 5(b) (6)

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Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation. Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[4], and a reduction in death or the need for oxygen at 28

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days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited

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ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While

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intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas within one hour of intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standardpractice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 $\geq$88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was

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known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. (Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or

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race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, $p=0.060$) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, $p=0.03$, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP

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infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[15] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven limited ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that early CPAP and protocol driven limited ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Avroy Fanaroff
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Fw: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 11:52:56 PM

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thanks
manuscript received- not yet read
Av

--- On **Sat, 11/7/09, Higgins, Rosemary (NIH/NICHD) [E] <*higginsr@mail.nih.gov*>** wrote:

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Subject: Fw: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
To: "(b) (6) <(b) (6)
Date: Saturday, November 7, 2009, 8:06 PM

Here is wally's paper

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Nancy Newman <nxs5@case.edu>; Susie Buchter <Susie.Buchter@oz.ped.emory.edu>; Brenda Morris (b) (6) Laroia, Nirupama <Nirupama_Laroia@URMC.Rochester.edu>; Sood, Beena <bsood@med.wayne.edu>; sduara@miami.edu <sduara@miami.edu>; Michael O`Shea <moshea@wfubmc.edu>; Anthony Piazza <Anthony.Piazza@oz.ped.emory.edu>; vineet.bhandari@yale.edu <vineet.bhandari@yale.edu>; Vivek.Narendran@cchmc.org <Vivek.Narendran@cchmc.org>; Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>; Luc.Brion@UTSouthwestern.edu <Luc.Brion@UTSouthwestern.edu>; rohls@unm.edu <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; ambal@uab.edu <ambal@uab.edu>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; ifrantz@tuftsmedicalcenter.org <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Michelle Walsh <mcw3@po.cwru.edu>; MIckey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOldberg <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Cunningham, Meg <mcunningham@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Sat Nov 07 07:40:08 2009
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

The O2 sat paper went out without figures due to some computer glitch. Here is a copy with the 2 figures.

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Director, Division of Neonatology

Director, Newborn Nurseries

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 3:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo , M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,

Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC

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communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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higginsr@mail.nih.gov

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From:	Wally Carlo, M.D.
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Carolyn Petrie
Subject:	RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date:	Saturday, November 07, 2009 7:53:47 PM
Attachments:	SUPPORT CPAP Manuscript - Network Version Word Nov 6 09.doc

Neil:

I am enclosing tracked changes.

I was reading the instructions for authors from NEJM and there are a few issues including the title limit to 75 characters, the recommendation to use the term randomized or something similar in the title or abstract, the word limit of 250 and 2700 for the abstract and text, respectively, the limited use of abbreviations, and trial number at the end of the title.

Great job.

Wally

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sat 11/7/2009 11:09 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; Shahnaz Duara; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Dale Phelps; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); Av Fanaroff; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Edward Bell; Ed Donovan; Ehrenkranz@Yale. Edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh-Sukys; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Ken Poole; Roger Faix; Duke. Edu>;; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Jon Tyson; VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Carolyn Petrie
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Again
The previous version was unreadable by most – Sorry for that
Here is a Word doc that I hope all can read
Neil

On 11/6/09 3:01 PM, "Neil Finer" <nfiner@ucsd.edu> wrote:

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,

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Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

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866-675-(b) (6) with passcode (b) (6)

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Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements (I sent several questions regarding the boilerplate to Stephanie for clarification with Wally's paper)

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven limited ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while ~~in the NICU and~~ receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001).

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Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and

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found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP for preterm infants with RDS in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] ~~The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation.~~ Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[14] However, the surfactant trials preceded widespread use of antenatal corticosteroids to promote lung maturation and the placebo groups did not received mechanical ventilation which could be injurious.

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group ~~(9.1~~(9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent

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with the findings of an earlier meta analysies[44], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006~~) with~~) with no statistically significant difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT Trial~~study~~ was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. (already stated)~~These results will be separately reported~~.

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The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven limited ventilator strategy in infants of 24 to 27~~8~~ weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, ~~-~~and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece ~~resuscitator or~~resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: ~~Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol,~~ CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% for one hour, an arterial $PaCO_2$ > 65 torr ~~documented on a single blood gas within one hour of intubation~~, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU ~~standardpractice~~standard practice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ ~~15 bpm~~15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and ~~be~~ hemodynamically ~~stable with~~stable without

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~~no~~ evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data)~~, and~~, and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61~~% using~~% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who

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required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1617]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. (Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

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There were 1316 infants enrolled in this trial from Feb 2005 through to Mar 1 ~~2009 .~~ 2009. Enrollment ~~The trial~~ was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post menstrual~~conceptional~~ age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, p=0.060) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental

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oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room, ~~nor any differences in~~ length of stay, ~~or~~ days of oxygen for survivors, or discharge on oxygen~~.~~ (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p<0=.00105). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non-significantly reduced in ~~in~~ the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a

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significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT Ttrial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant ~~given within an hour of life~~ in ELBW infants and the only prospective randomized trial comparing CPAP to any other intervention~~other outcome~~ that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our trial~~study~~ differs from the recently reported COIN trial[15~~15~~] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol

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driven limited ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven limited ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

Our study has demonstrated that early CPAP and protocol driven limited ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a ~~very~~ significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along ~~with reductions~~with reductions in BPD, ROP~~, significantly~~, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP ~~group without~~group without any increase in adverse neonatal ~~outcomes represents~~outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

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We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks~~, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium~~. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT Trial~~study~~ was a factorial design with each infant randomly ~~receiving 2~~receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven limited ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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From: Wally Carlo, M.D.
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Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: O2 sat paper
Date: Saturday, November 07, 2009 7:52:18 AM
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I am sending the attachment to you again as both of yours bounced back because of your spam filters.

The paper sent by Rose somehow lost the figures.

Wally

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

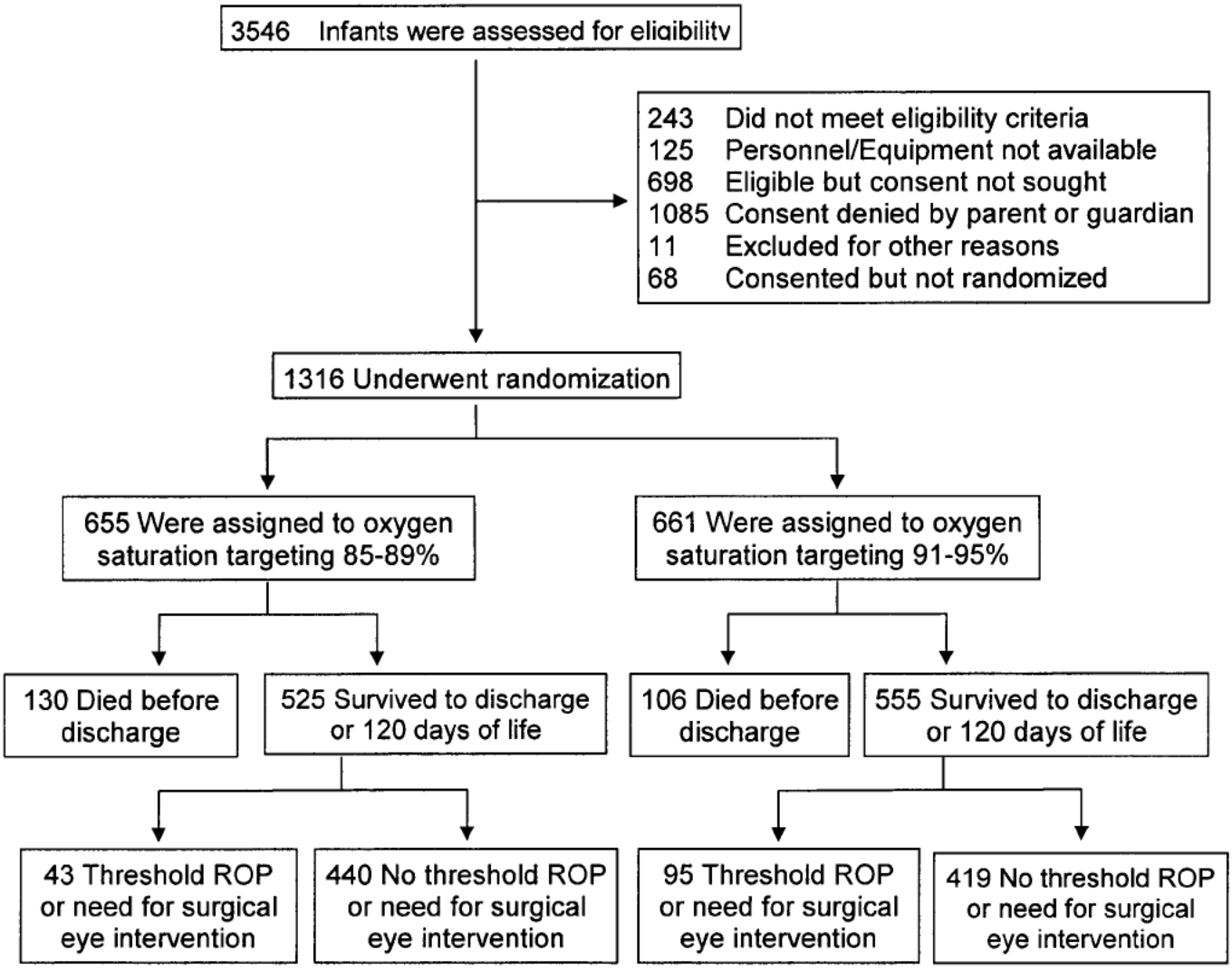

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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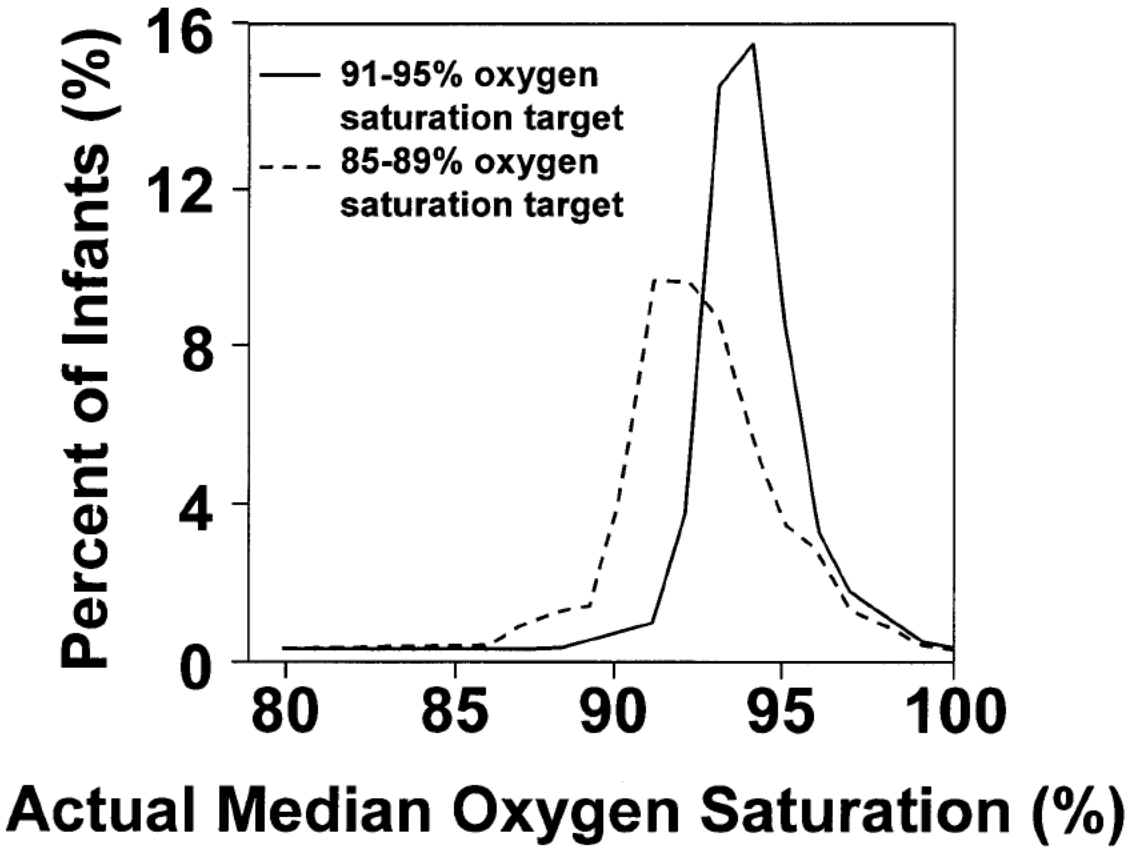
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject:	RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date:	Saturday, November 07, 2009 7:40:13 AM
Attachments:	Oxygen Saturation Target.11.6.09.MASTER.DOC

The O2 sat paper went out without figures due to some computer glitch. Here is a copy with the 2 figures.

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Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

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The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

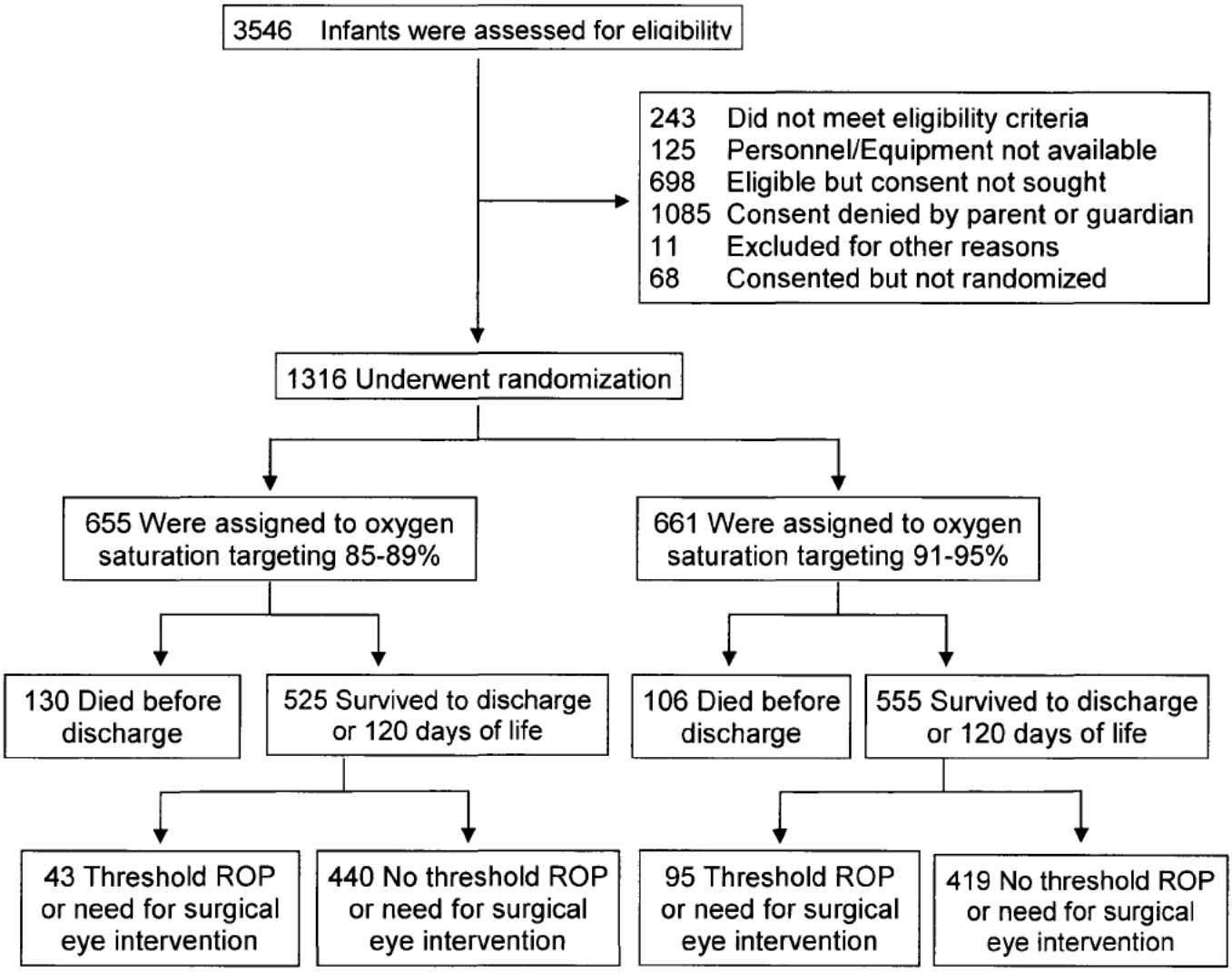

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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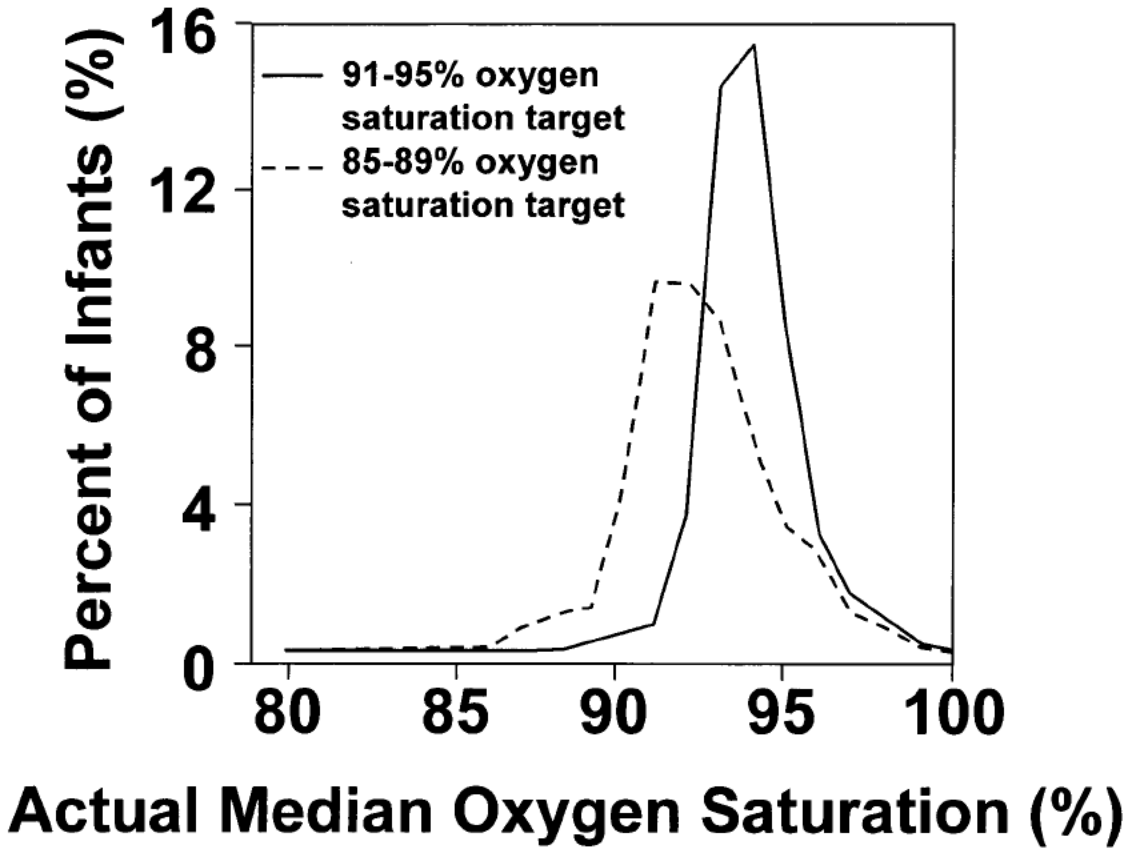
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Wally Carlo, M.D.
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Cc: nfiner@ucsd.edu
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 7:38:58 AM
Attachments: Oxygen Saturation Target.11.6.09.MASTER.DOC

For some reason, the manuscript O2 sat manuscript went without the figures. The enclosed draft has them (2).

Thanks for your prompt reviews.

Wally

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To: Ed Donovan; 'Fanaroff, Avroy'; Stevenson David (E-mail); jon.e.tyson@uth.tmc.edu
Cc: Wally Carlo, M.D.; nfiner@ucsd.edu
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,
You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

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Sent: Friday, November 06, 2009 4:42 PM
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Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks' gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

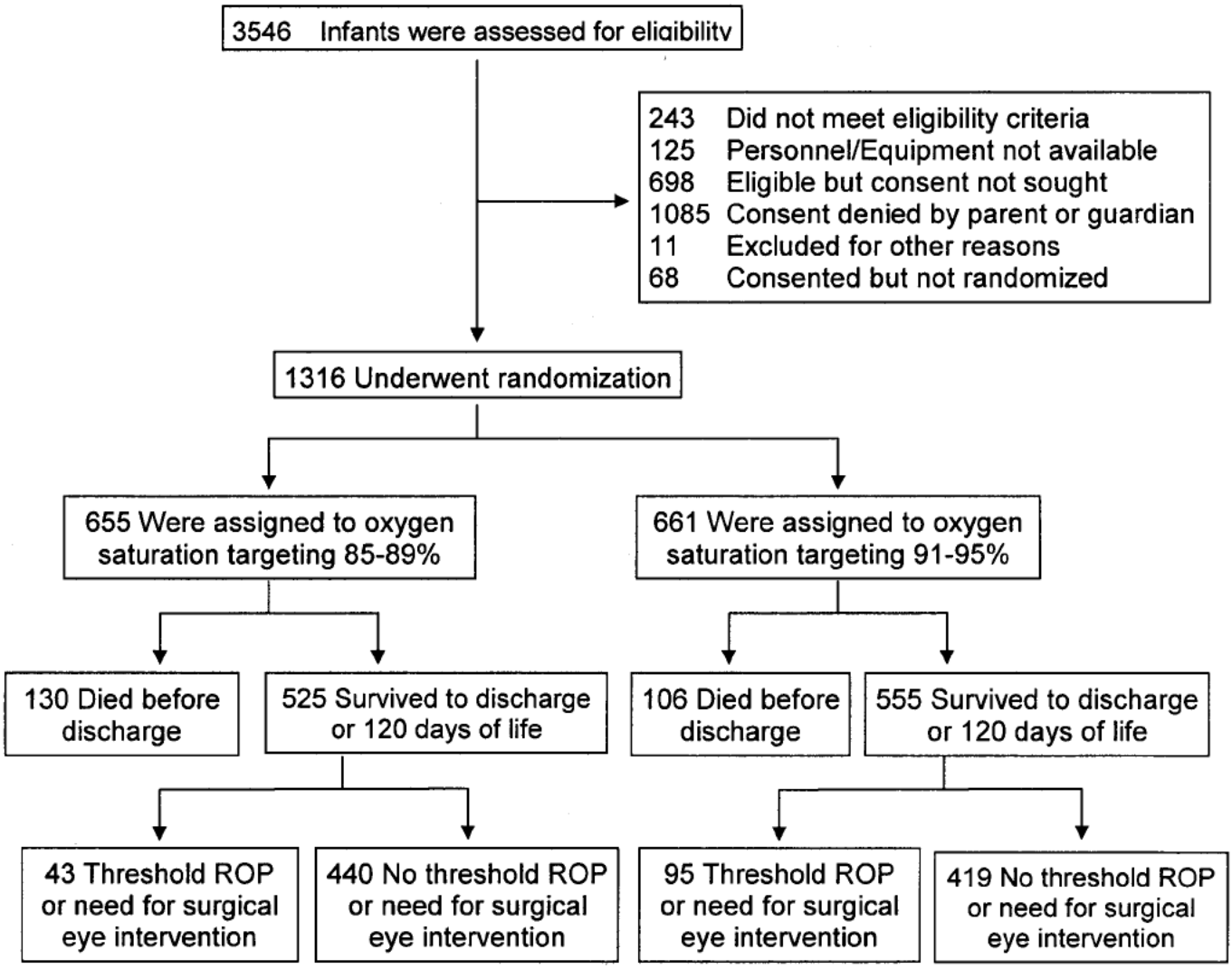

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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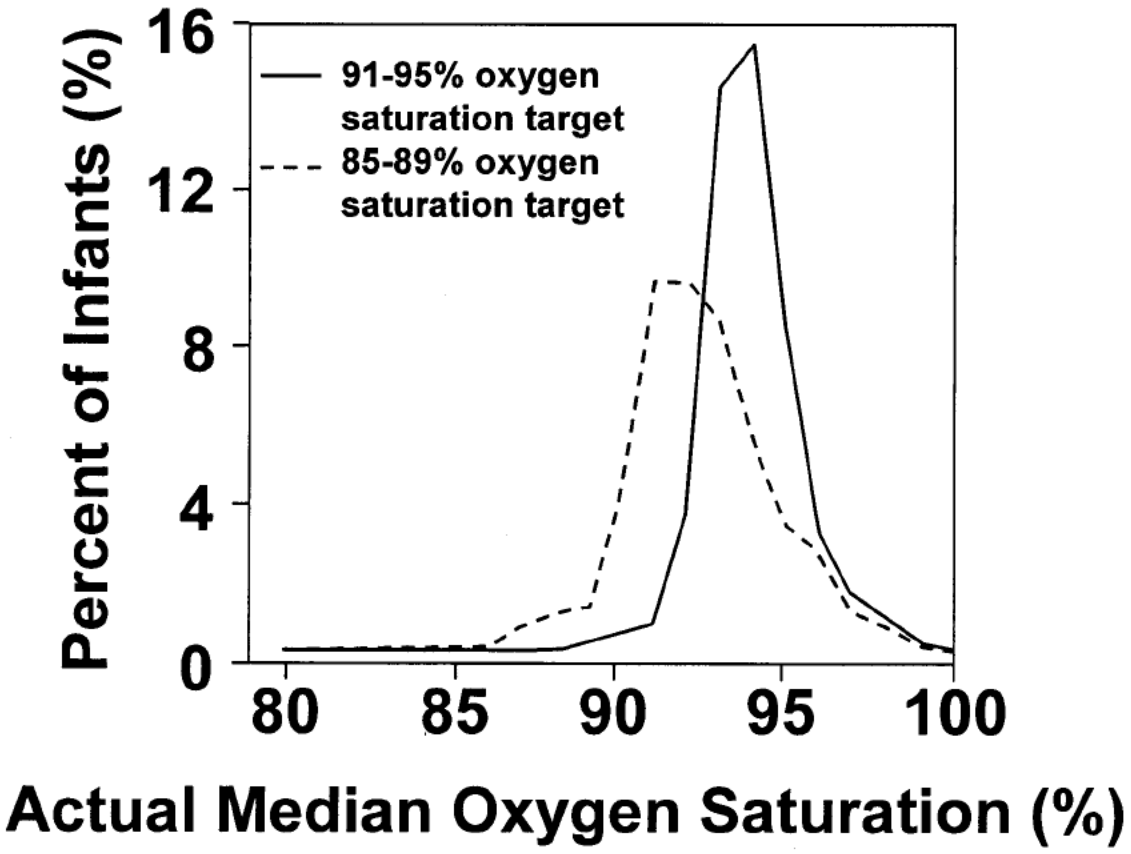
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 7:35:41 AM

Ok. Will do.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 07, 2009 6:34 AM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Those papers were the ones that both you and Neil sent. Can you and Neil hit "reply all" and resend the papers from your computers? I think this is a word 2007 issue.

Otherwise - can resend them on Monday once I have a patch installed by our IT folks for word 2007

Sorry for the trouble.
Av is the only one who asked for Figures. Ed bell had trouble opening the documents

Thanks
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Nov 07 07:11:39 2009
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Rose:

I noticed that neither of the two papers you attached have figures. I checked the one we sent you and it has. I forgot to add the legends.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 3:46 PM
To: Ed Donovan; 'Fanaroff, Avroy'; Stevenson David (E-mail); jon.e.tyson@uth.tmc.edu
Cc: Wally Carlo, M.D.; nfiner@ucsd.edu
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Ed, Av, Jon and David,
You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

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November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
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From: Fanaroff, Avroy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Saturday, November 07, 2009 12:20:22 AM

please resend manuscripts - they too have disappeared from my computer
we have had problems at work all week and have had no Internet access
Av

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 11/6/2009 4:41 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

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This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

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From: Wally Carlo, M.D.
To: Finer, Neil; Gantz, Marie
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT Subcommittee Meeting
Date: Friday, November 06, 2009 9:30:48 PM

Neil:
I agree.
wally

Wally Carlo, M.D.
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Director, Newborn Nurseries
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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 06, 2009 8:29 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: Re: SUPPORT Subcommittee Meeting

Hi Wally
I would not stress over this
I would suggest the following:
All surviving infants were followed by opthalmological specialists familiar with ROP until they had mature retina or until any observed ROP was deemed to have become quiescent or whatever wording is acceptable

We don't need to set a length in PCA
Neil

Sent from my iPhone

On Nov 6, 2009, at 3:13 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

> I'll have to look at the distribution of PMAs when final ROP status is
> obtained.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International

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> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 6:12 PM
> To: Gantz, Marie; Phelps, Dale; Finer, Neil; Higgins, Rosemary
> (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> I will have to change this in the methods.
>
> How late are the ROP outcomes followed?
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Gantz, Marie [mailto:mgantz@rti.org]
> Sent: Friday, November 06, 2009 4:51 PM
> To: Wally Carlo, M.D.; Phelps, Dale; Finer, Neil; Higgins, Rosemary
> (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> The ROP outcome is not just up to 55 weeks. Sometimes infants have
> reached final ROP status after that point.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 5:50 PM
> To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary
> (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> I got it. It is not predischarge only. I will fix the heading. In the
> text, it is stated that it the ROP outcome is to 55 weeks.
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics

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> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
> Sent: Friday, November 06, 2009 4:38 PM
> To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary
> (NIH/NICHD) [E]; Abhik Das; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> Not really. Many, if not most, infants were discharged long before
> 55
> weeks PMA. (table 3 shows medians of 99 or 102 days (= ~14 weeks).
> If
> the infants were median 26 weeks, they were discharged to home at
> median
> 40 weeks. No where near 55 weeks.
>
> You have listed ROP in the table of outcomes under the subheading:
> "Predischarge Outcome"
>
> That is my issue.
> Dale
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 2:23 PM
> To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary
> (NIH/NICHD) [E]; Abhik Das; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> Dale:
>
> We included the ROP outcomes up to 55 weeks PMA. Does that clarify
> your
> concern?
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
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>

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> -----Original Message-----
> From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
> Sent: Friday, November 06, 2009 3:35 PM
> To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary
> (NIH/NICHD) [E]; Abhik Das; Rich, Wade
> Subject: RE: SUPPORT Subcommittee Meeting
>
> Wally,
> The first thing I note is that the ROP is probably reported
> incorrectly.
>
> To the best of my understanding, the data provided to you by RTI is
> Threshhold ROP which occurred at any time. Some of these were after
> discharge.
>
> Dale
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, November 06, 2009 12:47 PM
> To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary
> (NIH/NICHD) [E]; Abhik Das; Rich, Wade
> Cc: Wally Carlo, M.D.
> Subject: RE: SUPPORT Subcommittee Meeting
>
> Dear SUPPORT Subcommittee members:
>
> Enclosed is a draft of the oxygen saturation paper for your
> comments. I
> need everyone's comments before we can submit to the Publications
> Subcommittee and the whole Steering Committee which gets it at the
> same
> time. I am also enclosing the first draft of the PAS abstract which
> is
> currently slightly above the word limit.
>
> Wally
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
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>

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Friday, November 06, 2009 7:13:24 PM

Correct Word 7
I will resend as an older doc or an RTF when I can – I am on call and we are busy
Neil

On 11/6/09 4:09 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Word documents (perhaps word 2007)

From: Bell, Edward <edward-bell@uiowa.edu>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 06 18:55:48 2009
Subject: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Neil,
What kind of file is the attachment? I can't open it.
Ed

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 06, 2009 5:01 PM
Subject: Re: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi Rose and Everyone
I cleaned up the previous version and accepted all Abhiks edits and made a few more corrections.
Please keep confidential
Look forward to your comments
Neil

On 11/6/09 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

The plan for submission is as follows:

November 16 – 4 PM – call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

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Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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Blansfield, Earl (NIH/NICHD) [E]

From: Gantz, Marie <mgantz@rti.org>
Sent: Friday, November 06, 2009 7:13 PM
To: Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: O2 Saturation Manuscript
Attachments: T2S Major Outcomes - 06NOV09.doc; T3S Other Outcomes - 06NOV09.doc.rtf; Cause of Death - 06NOV09.doc.rtf; T1S Baseline Characteristics - 06NOV09.doc.rtf

See below for some answers (in green). Others I'm still working on. New tables 1, 2, and 3 are attached, as are tables for cause of death (Table
1 and COD table have unadjusted p-values, all other p-values for outcomes are adjusted). Note that the DSMC was concerned about the "other" COD category. These are mostly cases where a terminal event rather than an underlying cause of death was recorded on the GDB forms.
We may have to query the centers to obtain more information. See the end of the COD document attached for "other" causes that have been moved into other categories, as well as those that are still in the "other"
category of the table. Please let me know if any adjustments to these categories need to be made. I have not updated any numbers in the text of Wally's paper yet, but I'll work on that and the other outstanding issues this weekend.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Das, Abhik
Sent: Friday, November 06, 2009 4:45 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Gantz, Marie
Subject: RE: O2 Saturation Manuscript

I have no problem with including that figure in a supplemental appendix.

Thanks

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Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 06, 2009 3:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Gantz, Marie; Das, Abhik
Cc: Wally Carlo, M.D.
Subject: RE: O2 Saturation Manuscript

Dear Rose, Neil, Marie and Abhik:

I have enclosed responses to Rose's comment below (red). I also incorporated Abhik's.

Abhik and Marie:

There are a few requests for you.

Thanks Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

Phone: 205 934 4680

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 11:23 AM

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To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'mgantz@rti.org'; 'adas@rti.org'
Cc: 'mcunningham@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'petrie@rti.org'
Subject: Re: Manuscript

Wally

Thanks for quickly turning this around.

We refer ro nonrandomized studies in several sections of the paper. Is observational a better word?

Sometimes "observational" may be ok but most studies were pre post studies (following a change in oxygen saturation targeting). These studies could be called "controlled" which is a better level of evidence than observational. I have been more specific in how I refer to those studies in the revised draft.

There is no citation of the STOP-ROP paper in the manuscript. Although this looked at saturation levels in pretheshold ROP, it should probably be listed.

It was quoted (ref 20) but the incorrect reference was put inadvertently in the reference list. This is now corrected. If we are below the NEJM word limit, I can add more details (especially that the intervention was late in the hospital course).

Methods - end of the first paragraph - delete "before delivery" as part of the consent process. Although this occrred in the vast majority, there were a few that occurred after delivery for a variety of reasons.

This happened because the protocol allowed it. I was trying to keep it short so may omit the details (exception).

Wold it be possible to include the scatter graph of actual versus monitor oximetry levels included in the stdy protocl in the supplementary/appendix materials? We explain this 3 percent offset in the methods on page 12, bt the graph really shows it to those who are visually oriented.

Abhik: What do you think?

At the bottom of page 12 we stated that sat targets were maintained by "clinicians.". It may be more accurate to say adjustments.... were performed by "NICU or clinical staff.". This way, everyone (nrse, md, resp therapist) are included and it is acucrate reporting.

Agree, change made.

In the methods section (page 13) nder assessments - should we (or do we even have space) report abot the 14 day safety monitoring??

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Rose: What should I say about the 14 day safety monitoring?

Leave 18-22 month FU out of the methods section on page 13 I this shold be incluuded in the discussion.

Moved to the Discussion section as suggested.

Bottom of page 14 I should we add one sentence about the first dsmc look at the data that occurred due to concern with compliance with sat levels are the part of the investigators as this happened prior to 25 percent enrollment? I suggest "dsmc evaluated sat data upon reqest of investigators to evaluate compliance after enrollment of XX infants.".
You do explain this in the results and it leaves the reader wondering why we did this.

Done

Results - first line page 15 I enrollment started in Feb 2005 not Jan 2004 (I think).

Marie: Can you check?

MG: First enrolled infant was in Feb 2005

Discussion - second line - you stated "standard" practice. I recommend changing this to "common" practice as there was no AAP guideline or otherwise indicating "standard."

Done

Page 17 - end paragraph- reviewers may want to know abot the lower sat infants and deaths (ron goldberg's comment at the sc meeting.

I think this will need further explanatory analysis. We may be able to address with Kaplan Meier plot and cause of deaths (which I have requested to Marie).

The last paragraph of the discussion should restate the primary outcome and the two significant otcones of ROP and BPD benefit.

Done, except BPD was only decreased when analyzed by O2 weaning, not by physiologic definition and the competing outcome of death eliminated the BPD benefit. Thus, I have not emphasized a BPD benefit.

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Table 1 has 655 in low sat group and 661 in high sat group. On table 2 many of the denominators are 654 in low sat group and there is a denominator of 662 on several of the high sat outcomes - we need to fix this.

Marie: Can you correct these? Can you also verify the figure numbers?

Also, threshold rop/death says 17/605 for low sat group (should be 170/) and high sat group says 198.616.

Corrected

Figure 1 - is there a way to have "pregnancies" assessed for eligibility?". That is actually how this nfolded.

Marie: Please check.

MG: We could convert certain numbers to pregnancies, but one of the problems is that those numbers are terrible to begin with. They do not account for pregnancies that were screened but did not result in deliveries that made it into the GDB or SUPPORT. If we want to give readers an accurate picture of how many women were screened/eligible we would be better off citing numbers from the Antenatal Consent study.

For figure 2 - is there any way to "statistically" assess if we reached an adequate separation between the two groups??
Marie: Can you analyze? I am sure they are statistically significant.

MG: A Rank Sums test of the difference of the medians of the two distributions in Figure 2 has a p-value of <0.0001.

Also -
I also pulled the May 2009 NeoProm confidential update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. I have spoken to NICHD and NHLBI leadership. The other trials are enrolling children following delivery. Our dsmc meets Nov 4 -the leadership would like input from or DSMC prior to any possible confidential dscussions with other dsmc's. Also the observed mortality between the two sat groups (16 and 20 percent) is tighter than the nrn range of mortality from historical data provided to our dsmc (9.5-32 percent deaths by day 14).

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>

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Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

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Cell: 205 266 (b) (6)

From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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Characteristic	Low SpO2 (N=654)	High SpO2 (N=662)	Relative Risk (of Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	171/605 (28)	198/616 (32)	0.9 (0.76, 1.06)	0.2050
ROP	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)	0.0001
Death at any time while hospitalized	130/654 (20)	107/662 (16)	1.27 (1.01, 1.6)	0.0412
Death in the first week	41/654 (6)	38/662 (6)	1.11 (0.72, 1.72)	0.6430
Death in the first 14 days	64/654 (10)	56/662 (8)	1.2 (0.84, 1.7)	0.3140
Death by 36 weeks PMA	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)	0.0610
BPD (supplemental O2)	203/540 (38)	265/568 (47)	0.82 (0.72, 0.93)	0.0020
BPD (supplemental O2) or death by 36 weeks PMA	317/654 (48)	359/662 (54)	0.91 (0.83, 1.01)	0.0754
BPD (physiologic definition)	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)	0.2339
BPD (physiologic definition) or death by 36 weeks PMA	319/654 (49)	331/662 (50)	0.99 (0.9, 1.1)	0.8988
IVH grade 3-4 (NG03)	83/630 (13)	81/640 (13)	1.06 (0.8, 1.4)	0.6997
Death or IVH grade 3-4 (NG03)	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)	0.0663
PVL (NG03 or MRI01)	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)	0.4996
Death or PVL (NG03 or MRI01)	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)	0.1102
Medical or surgical NEC (NG03)	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)	0.5076
Death or medical/surgical NEC (NG03)	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)	0.0746
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)	0.7104
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)	0.3876
PDA (any) (NG03)	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)	0.4320
PDA medical treatment (NG03)	219/634 (35)	233/645 (36)	0.95 (0.82, 1.09)	0.4689
PDA requiring surgery (NG03)	73/641 (11)	68/648 (10)	1.09 (0.8, 1.48)	0.5758
Pneumothorax (NG03 or SUPP08)	47/654 (7)	43/662 (6)	1.12 (0.74, 1.68)	0.6036
Any air leak in first 14 days (SUPP08)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)	0.2941
Postnatal steroids for BPD (NG03)	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)	0.5449
Postnatal steroids after DOL 21 (SUPP09)	123/650 (19)	140/661 (21)	0.91 (0.74, 1.12)	0.3850

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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SpO2 Paper Table 2. Other Outcomes for High vs. Low SpO2
Where GA is 24-25 weeks

Characteristic	Low SpO2 (N=276)	High SpO2 (N=289)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	117/256 (46)	139/271 (51)	0.88 (0.73, 1.05)	0.1648
ROP	34/176 (19)	68/201 (34)	0.58 (0.4, 0.84)	0.0039
Death at any time while hospitalized	85/276 (31)	73/289 (25)	1.24 (0.94, 1.64)	0.1225
Death in the first week	26/276 (9)	28/289 (10)	0.96 (0.57, 1.64)	0.8905
Death in the first 14 days	41/276 (15)	40/289 (14)	1.12 (0.73, 1.71)	0.6073
Death by 36 weeks PMA	75/276 (27)	64/289 (22)	1.26 (0.93, 1.71)	0.1370
BPD (supplemental O2)	101/201 (50)	127/225 (56)	0.89 (0.75, 1.04)	0.1471
BPD (supplemental O2) or death by 36 weeks PMA	176/276 (64)	191/289 (66)	0.97 (0.86, 1.1)	0.6547
BPD (physiologic definition)	105/201 (52)	128/225 (57)	0.91 (0.78, 1.07)	0.2645
BPD (physiologic definition) or death by 36 weeks PMA	180/276 (65)	192/289 (66)	0.99 (0.88, 1.11)	0.8024
IVH grade 3-4 (NG03)	47/263 (18)	52/275 (19)	0.98 (0.69, 1.4)	0.9012
Death or IVH grade 3-4 (NG03)	108/276 (39)	101/289 (35)	1.14 (0.92, 1.41)	0.2474
PVL (NG03 or MRI01)	13/263 (5)	18/275 (7)	0.78 (0.39, 1.58)	0.4956
Death or PVL (NG03 or MRI01)	95/276 (34)	88/289 (30)	1.16 (0.9, 1.48)	0.2467
Medical or surgical NEC (NG03)	39/269 (14)	38/278 (14)	1.05 (0.69, 1.59)	0.8369
Death or medical/surgical NEC (NG03)	104/276 (38)	98/289 (34)	1.13 (0.9, 1.42)	0.3079
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	124/258 (48)	133/269 (49)	0.97 (0.82, 1.15)	0.7232
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	168/276 (61)	174/289 (60)	1.01 (0.89, 1.16)	0.8466
PDA (any) (NG03)	146/269 (54)	154/278 (55)	0.99 (0.85, 1.14)	0.8827
PDA medical treatment (NG03)	106/265 (40)	110/276 (40)	1 (0.82, 1.21)	0.9683
PDA requiring surgery (NG03)	48/269 (18)	44/278 (16)	1.12 (0.78, 1.62)	0.5465
Pneumothorax (NG03 or SUPP08)	29/276 (11)	21/289 (7)	1.52 (0.86, 2.67)	0.1502
Any air leak in first 14 days (SUPP08)	31/276 (11)	19/289 (7)	1.69 (0.97, 2.93)	0.0633
Postnatal steroids for BPD (NG03)	46/266 (17)	44/274 (16)	1.06 (0.74, 1.52)	0.7503
Postnatal steroids after DOL 21 (SUPP09)	86/273 (32)	86/288 (30)	1.06 (0.83, 1.34)	0.6558

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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SpO2 Paper Table 2, Other Outcomes for High vs. Low SpO2
Where GA is 26-27 weeks

Characteristic	Low SpO2 (N=378)	High SpO2 (N=373)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted P-value
ROP or death	54/349 (15)	59/345 (17)	0.95 (0.67, 1.34)	0.7575
ROP	9/307 (3)	27/313 (9)	0.35 (0.17, 0.73)	0.0049
Death at any time while hospitalized	45/378 (12)	34/373 (9)	1.33 (0.88, 2.01)	0.1811
Death in the first week	15/378 (4)	10/373 (3)	1.51 (0.69, 3.33)	0.3017
Death in the first 14 days	23/378 (6)	16/373 (4)	1.38 (0.74, 2.55)	0.3091
Death by 36 weeks PMA	39/378 (10)	30/373 (8)	1.3 (0.83, 2.02)	0.2537
BPD (supplemental O2)	102/339 (30)	138/343 (40)	0.75 (0.62, 0.92)	0.0057
BPD (supplemental O2) or death by 36 weeks PMA	141/378 (37)	168/373 (45)	0.85 (0.71, 1)	0.0522
BPD (physiologic definition)	100/339 (29)	109/343 (32)	0.93 (0.75, 1.16)	0.5314
BPD (physiologic definition) or death by 36 weeks PMA	139/378 (37)	139/373 (37)	1 (0.83, 1.21)	0.9653
IVH grade 3-4 (NG03)	36/367 (10)	29/365 (8)	1.19 (0.74, 1.92)	0.4684
Death or IVH grade 3-4 (NG03)	71/377 (19)	55/372 (15)	1.27 (0.92, 1.75)	0.1443
PVL (NG03 or MRI01)	11/368 (3)	12/366 (3)	0.9 (0.4, 2.07)	0.8126
Death or PVL (NG03 or MRI01)	54/378 (14)	44/373 (12)	1.23 (0.85, 1.79)	0.2698
Medical or surgical NEC (NG03)	37/372 (10)	32/371 (9)	1.19 (0.75, 1.87)	0.4607
Death or medical/surgical NEC (NG03)	72/378 (19)	57/373 (15)	1.28 (0.93, 1.76)	0.1247
LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	104/366 (28)	93/365 (25)	1.11 (0.88, 1.4)	0.3978
Death or LOS (culture positive) with antibiotics 5+ days or meningitis (NG03)	132/378 (35)	117/373 (31)	1.11 (0.91, 1.35)	0.3202
PDA (any) (NG03)	161/372 (43)	170/370 (46)	0.93 (0.79, 1.09)	0.3644
PDA medical treatment (NG03)	113/369 (31)	123/369 (33)	0.91 (0.74, 1.11)	0.3463
PDA requiring surgery (NG03)	25/372 (7)	24/370 (6)	1.04 (0.6, 1.81)	0.8946
Pneumothorax (NG03 or SUPP08)	18/378 (5)	22/373 (6)	0.76 (0.41, 1.4)	0.3743
Any air leak in first 14 days (SUPP08)	20/378 (5)	23/373 (6)	0.87 (0.49, 1.55)	0.6303
Postnatal steroids for BPD (NG03)	15/370 (4)	25/370 (7)	0.64 (0.34, 1.19)	0.1567
Postnatal steroids after DOL 21 (SUPP09)	37/377 (10)	54/373 (14)	0.69 (0.47, 1.02)	0.0654

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.
Data from NG03 exclude infants who died in the first 12 hours.

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Characteristic	Category	Low SpO2 (N=654)	High SpO2 (N=662)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted p-value
Total LOS any hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1075)	104.5 ± 2.0	106.4 ± 2.0		0.4477
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean±StdErr (N=1079)	99.8 ± 2.0	103.0 ± 2.0		0.2175
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	25.5 ± 1.1	26.9 ± 1.0		0.3021
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	59.8 ± 1.6	67.4 ± 1.5		0.0002
Days on CPAP (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	17.1 ± 0.6	17.0 ± 0.6		0.9391
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean±StdErr (N=1098)	3.3 ± 0.3	3.8 ± 0.3		0.1362
Alive and off MV (HFV/CV) at 14 days (NG07 or SUPP05)		332/644 (52)	326/655 (50)	1.01 (0.91, 1.12)	0.8564
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		351/648 (54)	329/659 (50)	1.06 (0.96, 1.16)	0.2695

NOTE: Length of stay is up to one year (NG05 status)
NOTE: Duration of vent/O2/CPAP/nSIMV is up to 120 days (NG03 status)

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Variable	Category	CPAP (N=109)	Surfactant (N=128)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	22/109 (20)	40/128 (31)	0.2139
	2=BPD	12/109 (11)	12/128 (9)	
	3=Infection	26/109 (24)	20/128 (16)	
	4=NEC	14/109 (13)	23/128 (18)	
	5=CNS Insult	13/109 (12)	8/128 (6)	
	6=Immaturity	4/109 (4)	6/128 (5)	
	7=Other	18/109 (17)	19/128 (15)	

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Cause of Death for CPAP vs. Surfactant
Where GA is 24-25 weeks

Variable	Category	CPAP (N=68)	Surfactant (N=90)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	13/68 (19)	31/90 (34)	0.1212
	2=BPD	10/68 (15)	7/90 (8)	
	3=Infection	14/68 (21)	15/90 (17)	
	4=NEC	10/68 (15)	16/90 (18)	
	5=CNS Insult	11/68 (16)	5/90 (6)	
	6=Immaturity	3/68 (4)	5/90 (6)	
	7=Other	7/68 (10)	11/90 (12)	

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Cause of Death for CPAP vs. Surfactant
Where GA is 26-27 weeks

Variable	Category	CPAP (N=41)	Surfactant (N=38)	Unadjusted P-Value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	9/41 (22)	9/38 (24)	0.4750
	2=BPD	2/41 (5)	5/38 (13)	
	3=Infection	12/41 (29)	5/38 (13)	
	4=NEC	4/41 (10)	7/38 (18)	
	5=CNS Insult	2/41 (5)	3/38 (8)	
	6=Immaturity	1/41 (2)	1/38 (3)	
	7=Other	11/41 (27)	8/38 (21)	

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Variable	Category	Low SpO2 (N=130)	High SpO2 (N=107)	Unadjusted p-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	31/130 (24)	31/107 (29)	0.8018
	2=BPD	14/130 (11)	10/107 (9)	
	3=Infection	25/130 (19)	21/107 (20)	
	4=NEC	23/130 (18)	14/107 (13)	
	5=CNS Insult	12/130 (9)	9/107 (8)	
	6=Immaturity	7/130 (5)	3/107 (3)	
	7=Other	18/130 (14)	19/107 (18)	

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Cause of Death for Low vs. High SpO2
Where GA is 24-25 weeks

Variable	Category	Low SpO2 (N=85)	High SpO2 (N=73)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	23/85 (27)	21/73 (29)	0.4764
	2=BPD	8/85 (9)	9/73 (12)	
	3=Infection	16/85 (19)	13/73 (18)	
	4=NEC	17/85 (20)	9/73 (12)	
	5=CNS Insult	10/85 (12)	6/73 (8)	
	6=Immaturity	5/85 (6)	3/73 (4)	
	7=Other	6/85 (7)	12/73 (16)	

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Cause of Death for Low vs. High SpO2
Where GA is 26-27 weeks

Variable	Category	Low SpO2 (N=45)	High SpO2 (N=34)	Unadjusted P-value
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	8/45 (18)	10/34 (29)	0.4182
	2=BPD	6/45 (13)	1/34 (3)	
	3=Infection	9/45 (20)	8/34 (24)	
	4=NEC	6/45 (13)	5/34 (15)	
	5=CNS Insult	2/45 (4)	3/34 (9)	
	6=Immaturity	2/45 (4)	0/34 (0)	
	7=Other	12/45 (27)	7/34 (21)	

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Contributory cause of death (NG03e, NG03, NG05)=1=RDS

Obs	Other COD specified on NG03e, NG03 or NG05
1	extreme prematurity, RDS, suspected sepsis

Contributory cause of death (NG03e, NG03, NG05)=2=BPD

Obs	Other COD specified on NG03e, NG03 or NG05
2	bpd with multi-systaem organ failure,developed abd. compartment syndrome post-op stricture repair
3	Early onset sepsis & BPD w/severe intracranial hemorrhage.
4	PAHN, Liver Failure, CLD, Resp Failure
5	Endocarditis, Staph pneumonia, multiple pneumothoraces, cystic abscess in lung and advanced BPD
6	Cardiopulmonary arrest due to Pulmonary hypertension & Systemic hypotension & chronic lung disease

Contributory cause of death (NG03e, NG03, NG05)=3=Infection

Obs	Other COD specified on NG03e, NG03 or NG05
7	disseminated Candidiasis
8	pneumonia, sepsis (Blood and lung cultures (+) for S. Aureus, E. Cloacae)
9	proven NEC, sepsis, extreme prematurity
10	extreme prematurity, suspected pulmonary hypoplasia, pneumonia, presumed sepsis
11	ELBW, acute renal failure, severe lung disease, pneumonia, proven sepsis, hypocalcemia
12	septic shock, cardio-respiratory failure, renal failure
13	extreme prematurity, and sepsis
14	extreme prematurity, ecoli sepsis,meningitis
15	Pseudomonas sepsis, acute resp. failure, renal failure
16	pulmonary hypoplasia, clinical sepsis
17	suspected sepsis, DIC, and cerebellar hemorrhage
18	bilateral chylothoraces, sepsis, meconium peritonitis

Contributory cause of death (NG03e, NG03, NG05)=5=CNS Insult

Obs	Other COD specified on NG03e, NG03 or NG05
19	Severe IVH, Pulmonary hemorrhage, HMD, PIE
20	Severe IVH and Pulmonary Hemorrhage
21	Pulmonary hypoplasia with severe intraparenchymal IVH
22	Renal failure and Intraventricular hemorrhage

Contributory cause of death (NG03e, NG03, NG05)=6=Immaturity

Obs	Other COD specified on NG03e, NG03 or NG05
23	severe IUGR
24	prematurity, pulmonary hypertension,cardiorespiratory failure
25	extreme prematurity, severe pulmonary insufficiency

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Other causes of death specified by current classification in COD table

Contributory cause of death (NG03e, NG03, NG05)=7=Other

Obs	Other COD specified on NG03e, NG03 or NG05
26	extensive hemorrhage mid brain,brain stem,thalamic with uncal herniation and hydrocephaly
27	Respiratory failure
28	Pulmonary hemorrhage
29	liver failure
30	renal failure; DIC
31	liver failure with bleeding; ost. sites
32	PPHN-persistent pulmonary hypertension of neonate
33	intravascular hemorrhage before birth
34	per autopsy cause is exsanguination
35	pulmonary hypertension, pulmonary hypoplasia
36	pulmonary hypoplasia, chroramnionitis
37	Pulmonary Hypoplasia
38	twin to twin transfusion syndrome
39	massive pulmonary hemorrhage
40	pulmonary hemorrhage
41	pulmonary hypoplasia
42	Lung hypoplasia
43	hypoplastic lung syndrome due to pprom
44	Massive pulmonary hemorrhage without RDS
45	pulmonary hypoplasia due to multiple congenital anomalies
46	MULTI SYSTEM ORGAN FAILURE
47	severe hypoplastic lungs
48	renal failure;
49	severe pulmonary hypertension
50	tetralogy of fallot 7 other multiple cardiac anomalies renal anomalies(possiblby va cterl syndrome
51	cardiac arrythmia
52	extensive hemorrhage of rt. chest cavity after chest tube placement
53	perforation of right atrium by tip of PICC line
54	transposition of the great vessels
55	PREMATURITY, PULMONARY HYPOPLESIA, EXOPHAGEAL ATRESIA, SKELETAL ANNOMALIES
56	probable pulmonary hypoplasia

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Characteristic	Category	Low SpO2 (N=654)	High SpO2 (N=662)	Unadjusted p-value
Birth weight (grams)	Mean±StdDev (n=1316)	835.5 ± 193.4	824.8 ± 193.0	0.3138
Gestational age at birth (weeks)	Mean±StdDev (n=1316)	26.2 ± 1.1	26.1 ± 1.1	0.3925
Multiple birth (per NG02)		161/654 (25)	176/662 (27)	0.4134
Higher order multiple birth (3 or 4)		30/654 (5)	31/662 (5)	0.9343
Male		341/654 (52)	371/662 (56)	0.1556
Race/ethnicity	Non-Hispanic Black	257/654 (39)	232/662 (35)	0.2642
	Non-Hispanic White	242/654 (37)	279/662 (42)	
	Hispanic	132/654 (20)	127/662 (19)	
	Other/unknown	23/654 (4)	24/662 (4)	
Antenatal steroids (any)		633/654 (97)	632/661 (96)	0.2648
Antenatal steroids (full course)		477/651 (73)	462/658 (70)	0.2191
Apgar at 5 minutes <3		34/654 (5)	24/662 (4)	0.1644
Surfactant in DR or NICU (SUPP03, SUPP04)		531/653 (81)	558/660 (85)	0.1200

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SpO2 Paper Table 1 Baseline Characteristics for High vs. Low SpO2
Where GA is 24-25 weeks

Characteristic	Category	Low SpO2 (N=276)	High SpO2 (N=289)	Unadjusted p-value
Birth weight (grams)	Mean±StdDev (n=565)	705.3 ± 131.4	711.5 ± 133.7	0.5838
Gestational age at birth (weeks)	Mean±StdDev (n=565)	25.1 ± 0.6	25.1 ± 0.5	0.5518
Multiple birth (per NG02)		55/276 (20)	75/289 (26)	0.0890
Higher order multiple birth (3 or 4)		3/276 (1)	17/289 (6)	0.002*
Male		139/276 (50)	170/289 (59)	0.0434*
Race/ethnicity	Non-Hispanic Black	121/276 (44)	107/289 (37)	0.0974
	Non-Hispanic White	94/276 (34)	118/289 (41)	
	Hispanic	56/276 (20)	52/289 (18)	
	Other/unknown	5/276 (2)	12/289 (4)	
Antenatal steroids (any)		271/276 (98)	279/288 (97)	0.3163
Antenatal steroids (full course)		213/276 (77)	213/287 (74)	0.4136
Apgar at 5 minutes <3		22/276 (8)	16/289 (6)	0.2481
Surfactant in DR or NICU (SUPP03, SUPP04)		235/276 (85)	261/288 (91)	0.0457*

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SpO2 Paper Table 1. Baseline Characteristics for High vs. Low SpO2 Where GA is 26-27 weeks

Characteristic	Category	Low SpO2 (N=378)	High SpO2 (N=373)	Unadjusted P-value
Birth weight (grams)	Mean±StdDev (n=751)	930.5 ± 175.2	912.6 ± 186.1	0.1733
Gestational age at birth (weeks)	Mean±StdDev (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.6046
Multiple birth (per NG02)		106/378 (28)	101/373 (27)	0.7674
Higher order multiple birth (3 or 4)		27/378 (7)	14/373 (4)	0.0409*
Male		202/378 (53)	201/373 (54)	0.9020
Race/ethnicity	Non-Hispanic Black	136/378 (36)	125/373 (34)	0.5351
	Non-Hispanic White	148/378 (39)	161/373 (43)	
	Hispanic	76/378 (20)	75/373 (20)	
	Other/unknown	18/378 (5)	12/373 (3)	
Antenatal steroids (any)		362/378 (96)	353/373 (95)	0.4689
Antenatal steroids (full course)		264/375 (70)	249/371 (67)	0.3332
Apgar at 5 minutes <3		12/378 (3)	8/373 (2)	0.3808
Surfactant in DR or NICU (SUPP03, SUPP04)		296/377 (79)	297/372 (80)	0.6555

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; nfiner@ucsd.edu; Rich, Wade
Cc: Marsha Sumner
Subject: FW: Oxygen Saturation paper for your comments.
Date: Friday, November 06, 2009 6:46:12 PM
Attachments: Oxygen Saturation Target.11.6.09.MASTER.doc
SPR O2 Sats 11 6 09 (2).doc

I am sorry that my assistant did not send the email to the whole subcommittee (see below) .

The paper and the PAS draft are enclosed.

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-----Original Message-----
From: Wally Carlo, M.D.
Sent: Friday, November 06, 2009 4:33 PM
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Cc: Wally Carlo, M.D.
Subject: Oxygen Saturation paper for your comments.

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[l]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

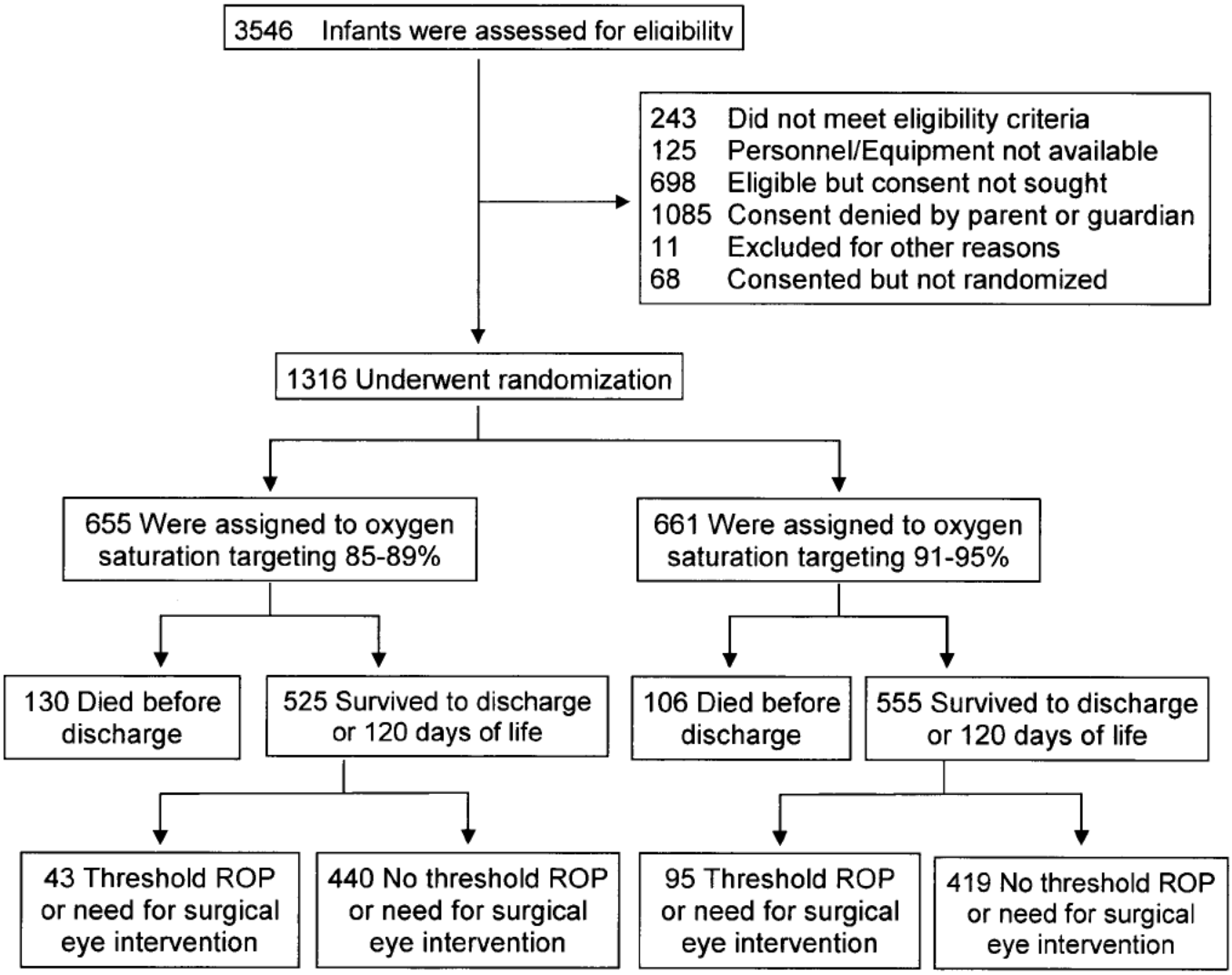

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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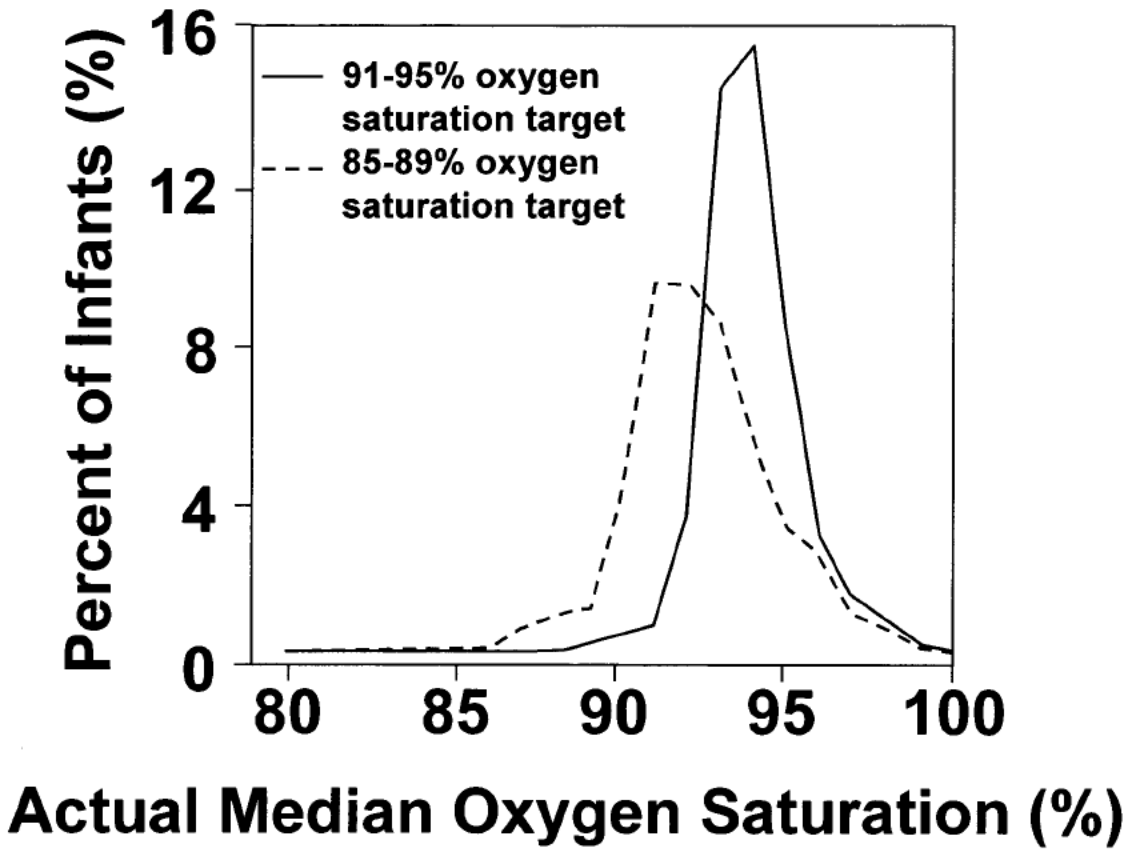
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants.

W.A. Carlo for the SUPPORT Subcommittee of the NICHD Neonatal Research Network.

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce retinopathy without increasing adverse outcomes.

Objective

To test the hypothesis that a lower oxygen saturation target decreases threshold retinopathy or deaths in extremely premature infants.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

-

Results

Threshold retinopathy/death did not differ between the oxygen saturation target groups (Table). Threshold retinopathy was decreased ($P<0.05$) in the lower oxygen saturation target group but death was more frequent ($P<0.05$, Table). Oxygen use at 36 weeks decreased in the lower oxygen

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saturation target group but oxygen use by the physiologic definition or oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups.

Conclusions

Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term retinopathy benefits.

Table:

	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)

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* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******
Date: Friday, November 06, 2009 5:59:36 PM

Will do.

Edward F. Donovan, M.D.
Ohio Perinatal Quality Collaborative
www.OPQC.net

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/6/2009 4:45 PM >>>
Hi Ed, Av, Jon and David,
You were included on the previous email and I am writing to ask a big favor.

We would like you to consider doing an internal review for these papers and providing me with written comments by 3 PM on 11/16. Let me know if your schedule permits. If you are not able to meet the time frame planned, let me know. There is urgency to submission of the papers.

Thanks in advance!!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 06, 2009 4:42 PM
To: nfiner@ucsd.edu; 'wrich@ucsd.edu'; Gantz, Marie; 'Nancy Newman'; 'Susie Buchter'; 'Brenda Morris'; 'Laroia, Nirupama'; Sood, Beena; sduara@miami.edu; 'Michael O`Shea'; Anthony Piazza; vineet.bhandari@yale.edu; 'Vivek.Narendran@cchmc.org'; Phelps, Dale; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: ****CONFIDENTIAL SUPPORT DRAFT MANUSCRIPTS*******

Hi,
Attached are the two papers in draft form for the SUPPORT Primary outcomes. As noted, there is an increase in death in the lower saturation group (20%) versus the higher saturation group (16%).

This information is confidential and a plan is in place for DSMC communication with ongoing trials of oxygen saturation. If you are contacted by any investigators from other trials or elsewhere, do not share this information. If necessary, refer them to me.

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The plan for submission is as follows:
November 16 - 4 PM - call for Steering committee and authors to discuss papers. In the meantime, feel free to send comments to Neil and Wally. The call in number is:
866-675-(b) (6) with passcode (b) (6)

If you are not going to be on the call, send comments in advance or designate someone to serve in your absence.

Immediately following the call, the manuscripts will be finalized for NICHD clearance and for submission to the New England Journal of Medicine.

Thanks in advance to everyone for all their hard work!!!
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Abhik Das
Subject: RE: SPR O2 Sats 11 6 09 (2)
Date: Friday, November 06, 2009 5:25:23 PM

Ok. I have asked Marie to check all #s.

Marie:

Please see comment below. Can you verify all the numbers?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
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Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 3:02 PM
To: Wally Carlo, M.D.
Subject: SPR O2 Sats 11 6 09 (2)

Wally
I am fine with this with the exception of the primary outcome numbers - the denominators add up to 1321 infants - this is NOT correct - can Marie check all the numbers in the table??
Thanks
Rose

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From: Wally Carlo, M.D.
To: Phelps, Dale; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT Subcommittee Meeting
Date: Friday, November 06, 2009 3:47:27 PM
Attachments: Oxygen Saturation Target.11.6.09.MASTER.doc
SPR O2 Sats 11 6 09 (2).doc

Dear SUPPORT Subcommittee members:

Enclosed is a draft of the oxygen saturation paper for your comments. I need everyone's comments before we can submit to the Publications Subcommittee and the whole Steering Committee which gets it at the same time. I am also enclosing the first draft of the PAS abstract which is currently slightly above the word limit.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Word count:

Abstract: 212

Manuscript: 2449

Running head: Oxygen saturation and outcomes of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

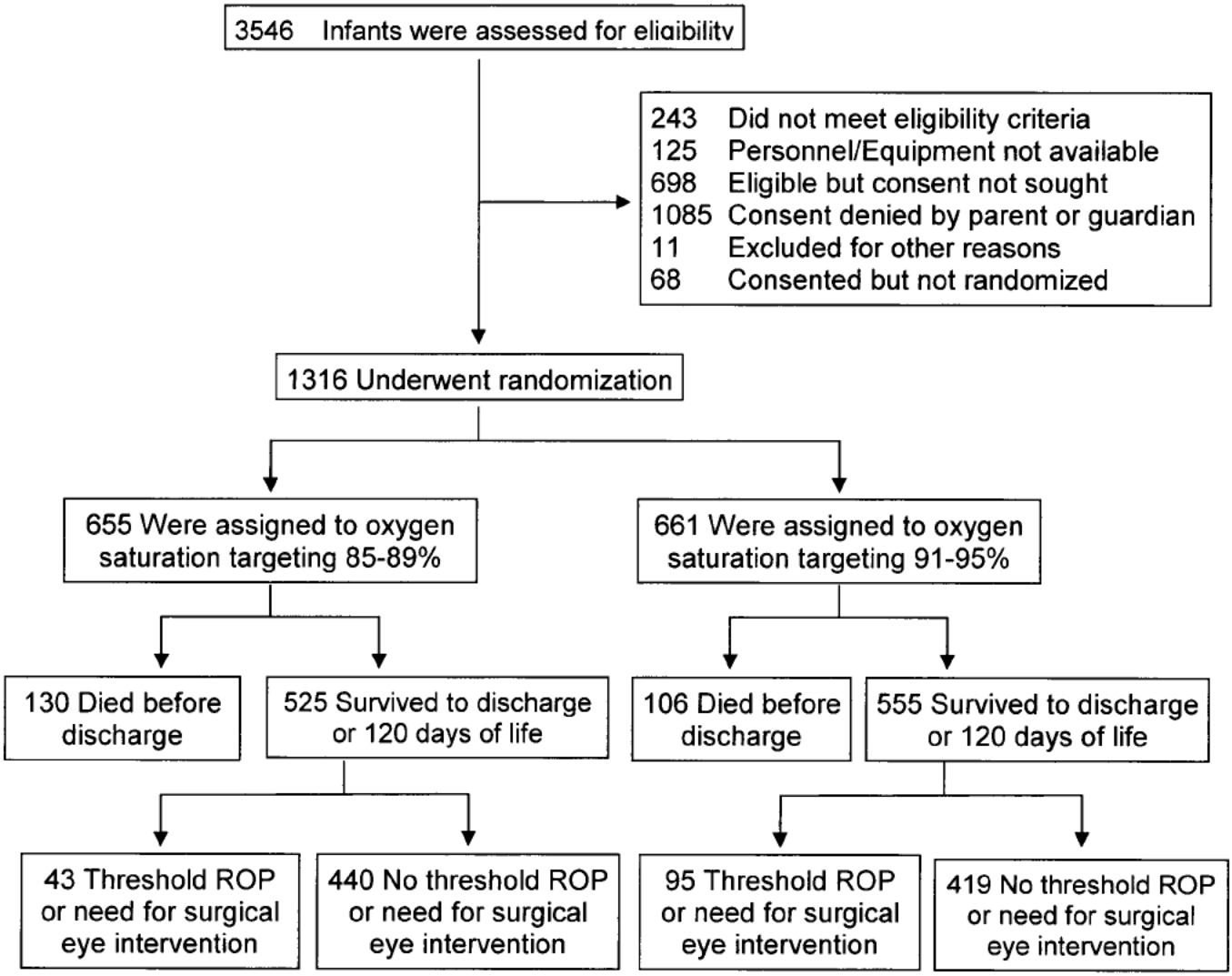

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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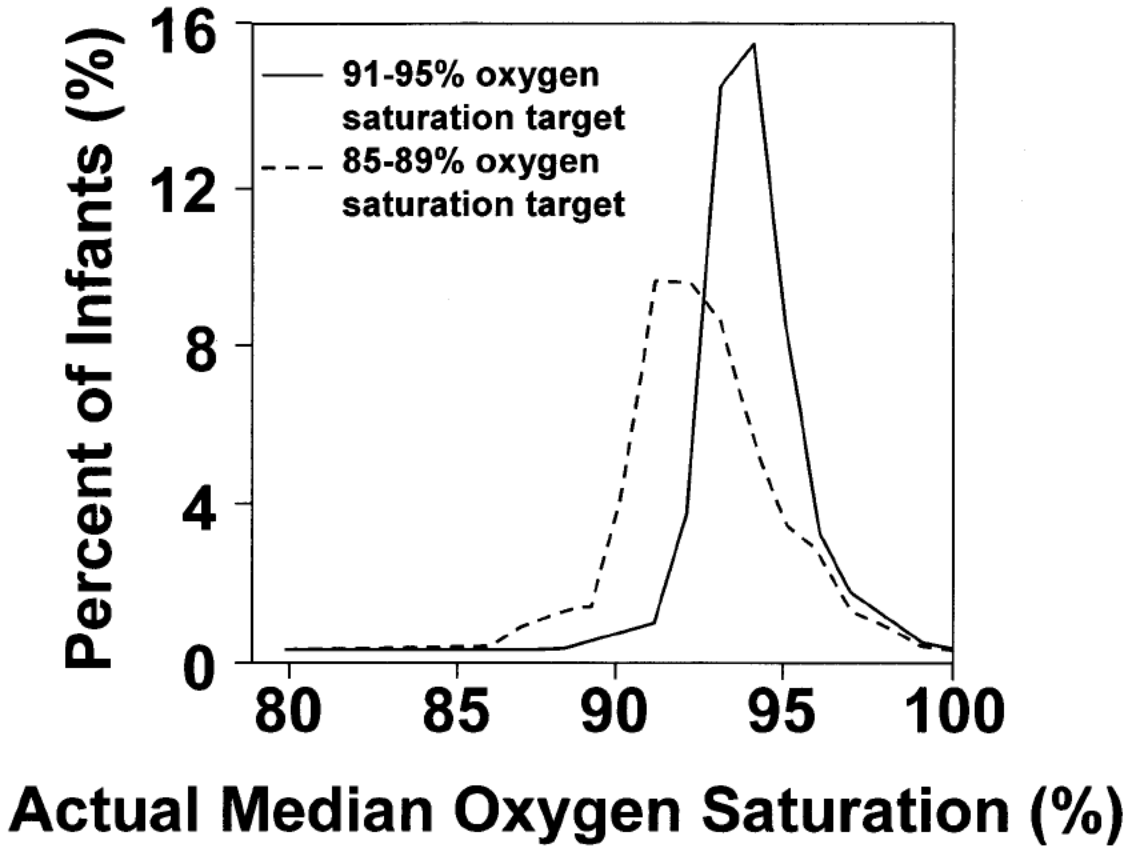
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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Title: Randomized Trial of Oxygen Saturation Targets in Premature Infants.

W.A. Carlo for the SUPPORT Subcommittee of the NICHD Neonatal Research Network.

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, it is important to determine if lower oxygen saturation targets reduce retinopathy without increasing adverse outcomes.

Objective

To test the hypothesis that a lower oxygen saturation target decreases threshold retinopathy or deaths in extremely premature infants.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95% using masked oximeters. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

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Results

Threshold retinopathy/death did not differ between the oxygen saturation target groups (Table). Threshold retinopathy was decreased ($P<0.05$) in the lower oxygen saturation target group but death was more frequent ($P<0.05$, Table). Oxygen use at 36 weeks decreased in the lower oxygen

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saturation target group but oxygen use by the physiologic definition or oxygen use at 36 weeks/death did not decrease. Other outcomes did not differ between the groups.

Conclusions

Lower oxygen saturation (85-89%) targets did not significantly decrease the combined outcomes of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly being advocated because it has short term retinopathy benefits.

Table:

	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)

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* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mgantz@rti.org; adas@rti.org
Cc: Wally Carlo, M.D.
Subject: RE: O2 Saturation Manuscript
Date: Friday, November 06, 2009 3:43:31 PM
Attachments: Oxygen Saturation Target.11.6.09.MASTER.doc

Dear Rose, Neil, Marie and Abhik:

I have enclosed responses to Rose's comment below (red). I also incorporated Abhik's.

Abhik and Marie:
There are a few requests for you.

Thanks Wally

Wally Carlo, M.D.
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Director, Division of Neonatology
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 11:23 AM
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'mgantz@rti.org'; 'adas@rti.org'
Cc: 'mcunningham@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'petrie@rti.org'
Subject: Re: Manuscript

Wally

Thanks for quickly turning this around.

We refer ro nonrandomized studies in several sections of the paper. Is observational a better word?
Sometimes "observational" may be ok but most studies were pre post studies (following a change in oxygen saturation targeting). These studies could be called "controlled" which is a better level of evidence than observational. I have been more specific in how I refer to those studies in the revised draft.

There is no citation of the STOP-ROP paper in the manuscript. Although this looked at saturation levels in pretheshold ROP, it should probably be listed.
It was quoted (ref 20) but the incorrect reference was put inadvertently in the reference list. This is now corrected. If we are below the NEJM word limit, I can add more details (especially that the intervention was late in the hospital course).

Methods - end of the first paragraph - delete "before delivery" as part of the consent process. Although this occrred in the vast majority, there were a few that occurred after delivery for a variety of reasons.
This happened because the protocol allowed it. I was trying to keep it short so may omit the details (exception).

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Wold it be possible to include the scatter graph of actual versus monitor oximetry levels included in the stdy protocl in the supplementary/appendix materials? We explain this 3 percent offset in the methods on page 12, bt the graph really shows it to those who are visually oriented.
Abhik: What do you think?

At the bottom of page 12 we stated that sat targets were maintained by "clinicians.". It may be more accurate to say adjustments.... were performed by "NICU or clinical staff.". This way, everyone (nrse, md, resp therapist) are included and it is acucrate reporting.
Agree, change made.

In the methods section (page 13) nder assessments - should we (or do we even have space) report abot the 14 day safety monitoring??
Rose: What should I say about the 14 day safety monitoring?

Leave 18-22 month FU out of the methods section on page 13 I this shold be incluuded in the discussion.
Moved to the Discussion section as suggested.

Bottom of page 14 I should we add one sentence about the first dsmc look at the data that occurred due to concern with compliance with sat levels are the part of the investigators as this happened prior to 25 percent enrollment? I suggest "dsmc evaluated sat data upon reqest of investigators to evaluate compliance after enrollment of XX infants.". You do explain this in the results and it leaves the reader wondering why we did this.
Done

Results - first line page 15 I enrollment started in Feb 2005 not Jan 2004 (I think).

Marie: Can you check?

Discussion - second line - you stated "standard" practice. I recommend changing this to "common" practice as there was no AAP guideline or otherwise indicating "standard."
Done

Page 17 - end paragraph- reviewers may want to know abot the lower sat infants and deaths (ron goldberg's comment at the sc meeting.
I think this will need further explanatory analysis. We may be able to address with Kaplan Meier plot and cause of deaths (which I have requested to Marie).

The last paragraph of the discussion should restate the primary outcome and the two significant otcones of ROP and BPD benefit.
Done, except BPD was only decreased when analyzed by O2 weaning, not by physiologic definition and the competing outcome of death eliminated the BPD benefit. Thus, I have not emphasized a BPD benefit.

Table 1 has 655 in low sat group and 661 in high sat group. On table 2 many of the denominators are 654 in low sat group and there is a denominator of 662 on several of the high sat outcomes - we need to fix this.

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Marie: Can you correct these? Can you also verify the figure numbers?

Also, threshold rop/death says 17/605 for low sat group (should be 170/) and high sat group says 198.616.
Corrected

Figure 1 - is there a way to have "pregnancies" assessed for eligibility?". That is actually how this nfolded.
Marie: Please check.

For figure 2 - is there any way to "statistically" assess if we reached an adequate separation between the two groups??
Marie: Can you analyze? I am sure they are statistically significant.

Also -
I also pulled the May 2009 NeoProm confidential update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. I have spoken to NICHD and NHLBI leadership. The other trials are enrolling children following delivery. Our dsmc meets Nov 4 -the leadership would like input from or DSMC prior to any possible confidential dscussions with other dsmc's. Also the observed mortality between the two sat groups (16 and 20 percent) is tighter than the nrn range of mortality from historical data provided to our dsmc (9.5-32 percent deaths by day 14).

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>
Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

Wally Carlo, M.D.
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University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

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From: Kathryn Fallon
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To: Wally Carlo, M.D.
Subject: Manuscript

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Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

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Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

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University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

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Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Running head: Oxygen saturation and outcomes of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p= ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; p= 0.__) while threshold retinopathy occurred less often in these infants (9 vs 18%; RR 0.51; CI 0.37, 0.71; p= ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcome of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly

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being advocated because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. While data from these recent prospective observational studies, retrospective studies, or controlled but not randomized studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at RTI, the independent data coordinating center, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation for which a decision had been made to provide full resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[17] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinical, not the research staff. Reports of displayed data by clinical center were provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2

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factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy.

Assessments

Research nurses recorded all data using standardized definitions included in the trial Manual of Operations. Data were collected until discharge except for retinopathy. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Other outcomes recorded included only predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for

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familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation value between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. The sample size calculations were based on the rate of death or threshold retinopathy of 50% in the Neonatal Research Network from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on an intracluster correlation of 0.12 in this outcome, the sample size was increased by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. The required sample size was increased by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the two factorial arms.

Intent-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided p value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. In addition, the Data Safety and Monitoring Committee, upon request of the investigators, evaluated the oxygen saturation data after enrollment of ____ infants to evaluate

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compliance with the protocol. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; RR 0.90; CI 0.76, 1.06; p=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; p=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was

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decreased in the lower oxygen saturation targeted group (9 vs 18%; RR 0.51; CI 0.37, 0.71; p=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from non-randomized studies, and restriction of oxygen supplementation is becoming the common practice.[3-5, 19] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in this large multicenter randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered to examine a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 20] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the use of the intervention starting at birth and continuing while oxygen supplementation was needed in the current trial may be related to the adverse outcome.

Recent meta-analyses of trials of restriction of oxygen supplementation based on trials conducted in the 1950s to the 1970s showed a large reduction in severe retinopathy (RR 0.19; CI 0.07, 0.50).[1,21] There

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have not been other randomized controlled trials of different oxygen targeting starting soon after birth to reduce retinopathy. However, results of most non-randomized studies show that lower oxygen saturation targeting reduces retinopathy of prematurity. The current trial confirmed that lower oxygen targeting results in a large reduction of severe retinopathy.

In summary, lower oxygen saturation targeting did not affect the combined outcome of threshold retinopathy/death but increased mortality and decreased threshold retinopathy. There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[22] These trials use the same algorithms for oxygen saturation targeting so their data will be easy to combine in a meta-analysis to determine short and long term effects of oxygen saturation targeting. At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Neurodevelopmental assessments are being performed at 18-22 months corrected age. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	170/605 (28)	198/616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.60)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2 use) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.90, 1.10)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.80, 1.40)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.80, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (6)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

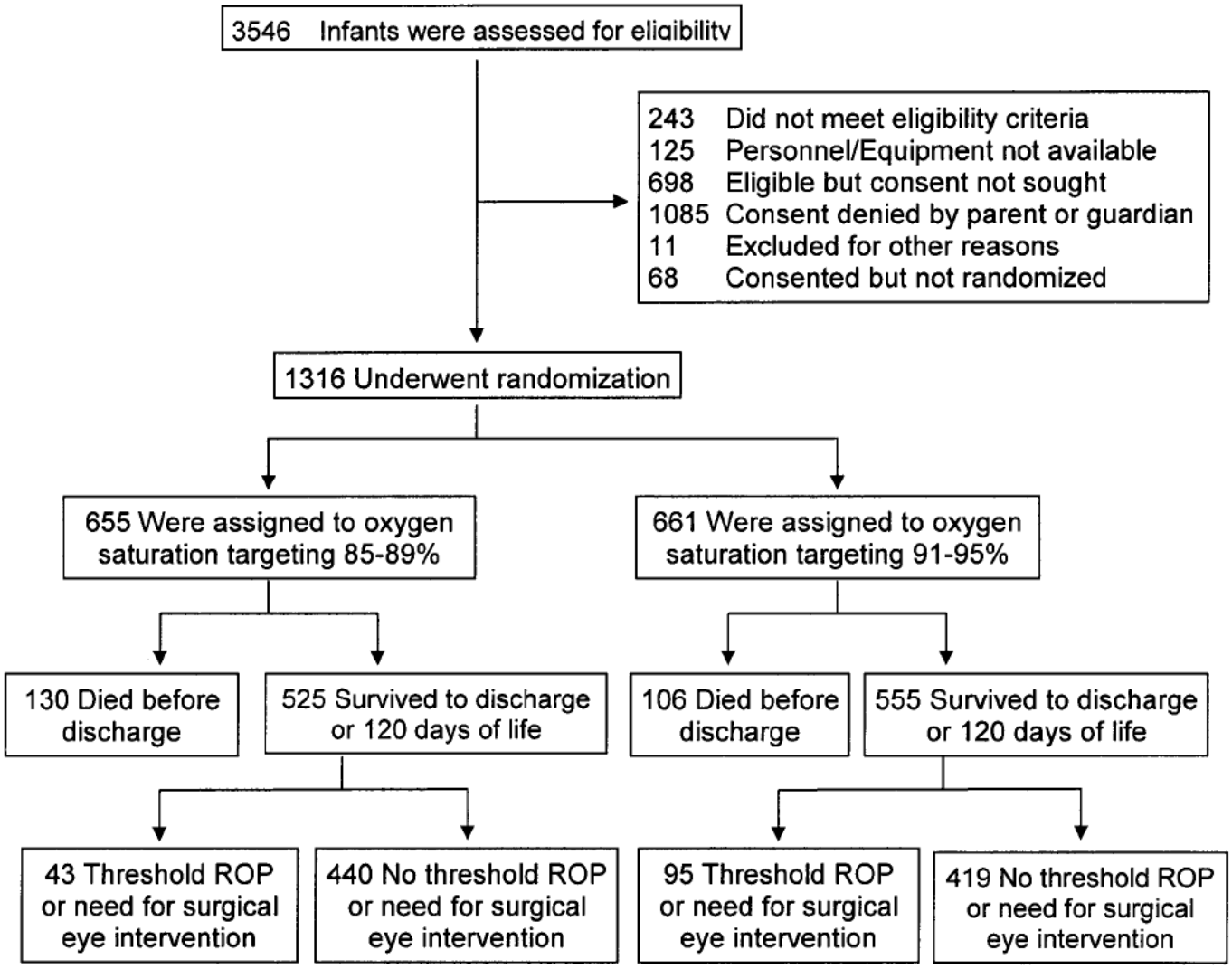

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Figure 2 Kaplan Meier plot for mortality (from Marie)

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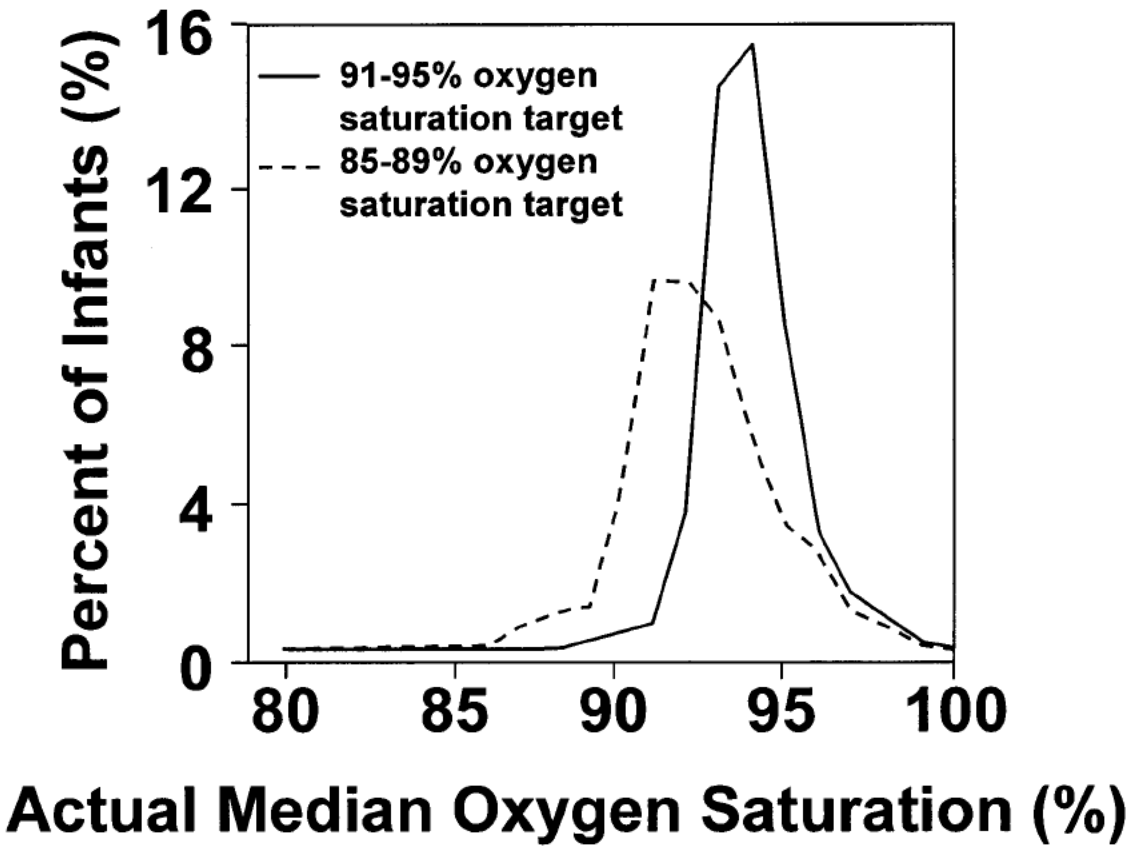
Figure 3



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, November 06, 2009 12:22:29 PM
Attachments: info to share.pdf

Here is the document; I only made some cosmetic changes to the one I sent to you earlier. So, Kris is going to initiate the process of establishing preliminary contact with these chairs.

Since we are sending this on behalf of NICHD, would you like to draft a short accompanying message?

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 06, 2009 11:53 AM
To: Das, Abhik
Subject: SUPPORT

Did you finalize the document for the other DSMC chairs from the SUPPORT data?? I have Deputy Director Concurrence that this needs to go to the chairs. We need a copy for approval/records

Thanks
Rose

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Selected Information from The Fourth Data Safety and Monitoring Committee Report for The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

November 4, 2009

Prepared by the NICHD Neonatal Research Network Data Center at RTI International, Research Triangle Park, NC

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A. Methods and Procedures

Study Design

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (NRN). The individual factors to be tested are:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant no longer requires ventilatory support or oxygen.

The oxygen saturation monitoring portion of the study is designed to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters that are calibrated to provide actual SpO2 values when the SpO2 is < 85% and > 95%. This methodology provides clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Primary Hypotheses

1) Relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks postmenstrual age (PMA).

2) Relative to infants managed with a higher SpO2 range, the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

Secondary Hypotheses

Use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decrease in mortality or neurodevelopmental impairment (NDI) at 18-22 months corrected age
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decrease in the percentage of infants who receive postnatal steroids for BPD
- A decreased incidence of BPD at 36 weeks PMA
- A decreased incidence of threshold ROP and/or the need for surgical intervention
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of intraventricular hemorrhage (IVH) and severe IVH
- A decreased incidence of periventricular leukomalacia (PVL)
- A decreased incidence of NDI at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up

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Study Population

Study subjects are infants of 24 0/7 to 27 6/7 weeks gestational age (GA) at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) are enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. There are 2 randomization strata, infants of 24 0/7 to 25 6/7 weeks GA, and infants of 26 0/7-27 6/7 weeks GA by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study is not powered to detect outcome differences between strata.

Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

Sampling Recruitment and Screening Procedures

Infants are recruited for this study by approaching parent(s) at the time of hospital admission when there is a perceived risk of premature delivery at 27 6/7ths weeks or less.

Sample Size

The required sample size for this trial was determined to be 1,310 to ensure 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. These results were based on observed prevalence of these outcomes in the Network Generic Data Base (GDB, a registry of all <1500 g births in the Network), and corrected for two primary outcomes (assumed significance level of 2%), for a clustering effect because of multiples being randomized to the same treatment, as well as for attrition. Note that this sample size is not sufficient to permit detection of interaction effects between the two treatments with reasonable power.

Randomization

Randomization is stratified by study site and gestational age group, occurs prior to delivery for consented deliveries, and is performed by utilizing specially prepared double-sealed envelopes. Deliveries are randomized as a unit, thus multiples, twins, triplets etc are randomized to the same arm of the trial. Appropriate sample size adjustments have been made to account for this clustering effect.

Study Intervention

The intervention begins after birth when the infant is given to the resuscitation team. The conduct of the resuscitation follows usual guidelines, and once stabilized, all Control infants in the Ventilation arm receive prophylactic/early surfactant (within 1 hour of age) whereas all

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Treatment infants are placed on CPAP/PEEP following stabilization and intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment is performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission. There are two ranges of SpO2 utilized during this trial. The Low target range is 85% to 89% and the High target range is 91% to 95%. The altered Pulse Oximeters (PO) display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO reads 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO displays 88% when the actual SpO2 is 91% and indicates 92% when the actual SpO2 is approximately 95%.

Interim Monitoring Plan

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion using interim monitoring boundaries. Efficacy is measured at approximately 25%, 50%, 75%, and 100% of outcome assessment. Primary outcomes are analyzed at these time points by statistically adjusting for familial clustering and stratification by gestational age stratum and center. To control for the inflation of Type I error associated with sequential testing, O'Brien-Fleming[1] boundaries are calculated using a Lan-DeMets[2] spending function. Safety is monitored at these time points as well using Pocock[3] boundaries for adverse event monitoring.

B. Selected Results

Enrollment

This is an extract from the report prepared for the final planned DSMC look at 100% of the primary outcome data for the SUPPORT Trial. As of February 2009, 1,316 infants have been enrolled in SUPPORT, exceeding the total expected enrollment of 1,310.

Treatment Compliance in Oxygen Saturation Arm

In the oxygen saturation arm, target saturation ranges are 85-89% and 91-95% for the Low and High SpO2 arms, respectively. **Table I** shows the percent of time infants on supplemental oxygen spent in various SpO2 ranges. Supplemental oxygen is defined as FiO2>.21 during the first 14 days of life (FiO2 is reported every two hours) or as documented oxygen use from day of life 15 through 36 weeks (oxygen use is recorded every 6 hours).

Time on supplemental oxygen	Oxygen saturation arm	Percent in narrow target 88-92 (Display)	Percent <84	Percent 84-96	Percent >96
Days of life 1-14	Low SpO2	19.7	11.8	76.2	12.0
	High SpO2	49.3	6.3	79.5	14.2
Day 15 to 36 wks	Low SpO2	15.5	15.4	67.1	17.6
	High SpO2	37.0	10.5	67.7	21.8

Table I Distribution of Time in SpO2 Display Ranges while on Supplemental Oxygen

Separation in Oxygen Saturation Arm **Table II** and **Figure I** address treatment separation in the Oxygen Saturation arm of the SUPPORT Trial. **Table II** shows the amount of time infants in

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each treatment group spend in room air. Only data from March 2006 to the present are included in Table 3.b, because since that time supplemental oxygen use has been recorded every two hours for day of life (DOL) 1-14 and every 6 hours thereafter. These data indicate some separation between the two treatment groups.

	DOL 1-14		DOL 15+	
	High SpO2	Low SpO2	High SpO2	Low SpO2
Hours in room air (hours in thousands)	35% (57/162)	46% (71/157)	35% (213/600)	46% (254/552)

Table II Percent of Time Spent in Room Air Since March 2006, by Treatment and Day of Life

Figure I shows the distribution of SpO2 values during time spent on supplemental oxygen for infants in the Low and High SpO2 target groups through 36 weeks PMA. There is modest separation between the groups, along with substantial overlap. The area under the overlapping portions of the curves is 85%. Thus, 15% of the area under each curve does not overlap the other.

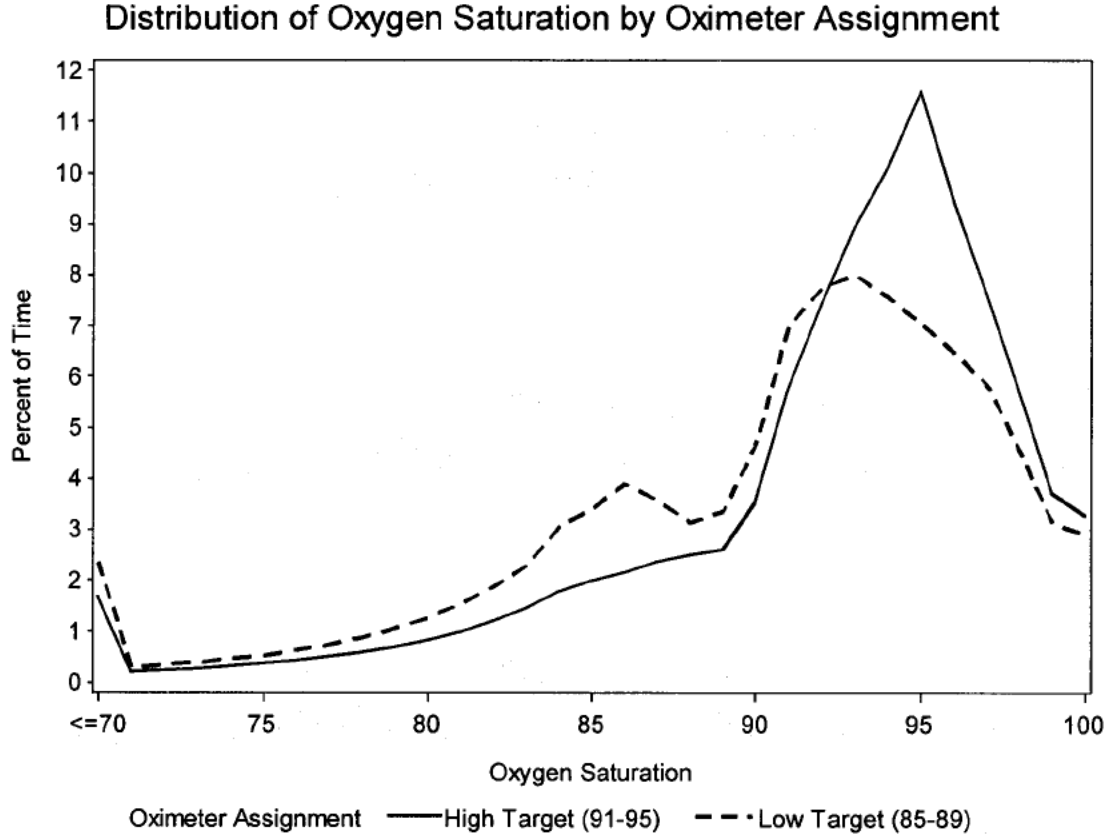

Figure I Percent of Time Spent at Each SpO2 Value for Infants in Low and High Target Groups (Includes only time on supplemental oxygen through 36 weeks PMA)

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Mortality Information

Table III show the percent of infants in each treatment group who died during the course of the SUPPORT Trial. The table also displays adjusted p-values for statistical tests comparing the percent of infants who died in each level of the two treatment factors. The tests are adjusted for familial clustering due to multiple births and for stratification by center and gestational age group. There is a statistically significant difference in the death rate between treatments in the oxygen saturation arm, with higher mortality in the low SpO2 arm.

Outcome	Oxygen Saturation Arm		Adjusted P-value
	Low SpO2 (N=654)	Low SpO2 (N=654)	
Death	20% (130/654)	16% (107/662)	0.0412

Table III Death in the Oxygen Saturation Arm

Gestational age was a significant predictor of death in the tests presented in Table III ($p<0.0001$). **Table IV** presents the mortality information by gestational age stratum. Note that the 26-27 week gestational age stratum includes three infants born at 28 weeks gestational age.

Gestational Age Strata	Oxygen Saturation Arm		Adjusted P-value
	Low SpO2	High SpO2	
GA 24-25 weeks (N=565)	31% (85/276)	25% (73/289)	0.1225
GA 26-27 weeks (N=751)	12% (45/378)	9% (34/373)	0.1811

Table IV Death in the Oxygen Saturation Arm by Gestational Age Group

Cause of Death **Table V** lists causes of death by treatment and gestational age group to address safety concerns regarding RDS and other factors contributing to mortality.

Cause of Death	Low SpO2		High SpO2	
	24-25 wks (N=85)	26-27 wks (N=45)	24-25 wks (N=73)	26-27 wks (N=34)
RDS	27% (23/85)	18% (8/45)	29% (21/73)	29% (10/34)
BPD	9% (8/85)	13% (6/45)	12% (9/73)	3% (1/34)
Infection	19% (16/85)	20% (9/45)	18% (13/73)	24% (8/34)
NEC	20% (17/85)	13% (6/45)	12% (9/73)	15% (5/34)
CNS Insult	12% (10/85)	4% (2/45)	8% (6/73)	9% (3/34)
Immaturity	6% (5/85)	4% (2/45)	4% (3/73)	0% (0/34)
Other	7% (6/85)	27% (12/45)	16% (12/73)	21% (7/34)

Table V Cause of Death, by Oxygen Saturation Treatment and GA at Birth

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1 O'Brien, P. C. and Fleming, T. R. (1979), A multiple testing procedure for clinical trials. Biometrics, 35, 549-556.

2 Reboussin, D. M., DeMets, D. L., Kim, K. and Lan, K. K. G. (2000), Computations for group sequential boundaries using the Lan-DeMets spending function method. Controlled Clinical Trials, 21, 190-207.

3 Pocock, S. J. (1977), Group sequential methods in the design and analysis of clinical trials. Biometrika, 64, 191-199.

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: LBJ
Date: Friday, November 06, 2009 10:28:12 AM

LBP? If you mean LBJ, that's correct.
Kathleen A. Kennedy, MD, MPH
Director, Neonatal-Perinatal Division
Director, MS in Clinical Research Degree Program

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Tyson, Jon E; Kennedy, Kathleen A
Cc: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>
Sent: Fri Nov 06 09:25:13 2009
Subject: LBJ

Jon and Kathleen – Georgia tells us that LBP was not included in SUPPORT – please verify this with me as I want to have an accurate boilerplate

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Wally Carlo, M.D.
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: adas@rti.org; mgantz@rti.org
Subject: RE: Manuscript
Date: Thursday, November 05, 2009 5:40:28 PM

Stephanie:

ok. I will wait to get the final one.

Wally

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thu 11/5/2009 4:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'nfiner@ucsd.edu'; Wally Carlo, M.D.
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: RE: Manuscript

See below...

I'm waiting on additional information for the items in green highlight.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, October 31, 2009 12:23 PM
To: Archer, Stephanie (NIH/NICHD) [E]; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: Urgent;Fw: Manuscript

Stephanie
I looked at the boilerplate in detail for Wally's paper.
I will repoll the steering committee regarding CTSA support and this will need to be accurately updated.
SWA: I'll make any changes once all votes are in. Still missing info from Case and Emory. I took out Indiana's and Utah's per PI responses. Have kept in Yale's, Stanford's, and Iowa's.

Emory has indicated an alternate author.
SWA: Changed

For individual site grant numbers, please list the U10 awards first (they funded the vast majority of study costs, the GCRCs and CTSA funding was much less).
SWA: Done

Please affirm/check the following items:
Mickey's institution name - I believe this is North Shore, but check with him or his staff. Also his tenure for the NRN should be 2006-present in stead of 2011.
SWA: No change, per Mickey.

Did indiana indicate that
Faithe Hamer had a role (in addition to FU)?
SWA: Sent Leslie a question about this.

RTI listing should also include Dennis Wallace, PhD.
SWA: Done

Does UCSD need to include Rene Bridges? She responded to several of the queries I sent over time.

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SWA: Done, per Wade Rich.

Does Iowa need to list Gretchen - one of the other research nurses?
SWA: Ed does NOT believe she should be included.

University of New Mexico - Conra Lacy is not listed, yet she is the lead coordinator. -please check.
SWA: Done, per Kristi.

UT southwestern - Diana Vasil is not listed and has also been involved with query resolution.
SWA: Sent Pablo a question about this.

The DSMC is missing and needs to be listed.
SWA: Done

We should also list the NHLBI folks. I will get a list of them.
SWA: Waiting to hear back from NHLBI.

Ask the houston site if any recruitment occured at LBJ hospital.
SWA: LBJ did NOT participate, per Georgia.

Let me know if you need help getting responses. This is a pivotal trial and I want to get it right.

Thanks so much for putting this together.

Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>
Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100

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Cell: 205 266 (b) (6)

From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT!
Date: Wednesday, November 04, 2009 2:36:00 PM

Should this come from us, or Dr. Gleason, or you?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 04, 2009 2:30 PM
To: Das, Abhik
Cc: Gantz, Marie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT!

Once our Director signs off on it, we would like RTI to confidentially send the information (so that it goes from DSMC to DSMC).

For the DSMC chairs for the various trials, I have:
BOOST II Australia and BOOST II New Zealand:
Professor Stephen MacMahon (smacmahon@george.org.au)

BOOST II UK:
Sir Iain Chalmers (ichalmers@cochrane.co.uk)

COT (Canadian Oxygen Trial)
Dr. William Fraser (William.fraser@umontreal.ca)

I would also request that you verify with each person that they are the chair of the DSMC prior to the confidential information being shared.

Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, November 04, 2009 2:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT!

I will work on it.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 04, 2009 1:58 PM
To: Das, Abhik
Cc: Gantz, Marie; Zaterka-Baxter, Kristin
Subject: SUPPORT!

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Abhik
Could you get us a brief summary of the information to be shared with the other dsmc's today so the NIH Director can review??

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

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From: Zaterka-Baxter, Kristin
To: Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Cc: Das, Abhik; Gantz, Marie; Cunningham, Meg
Subject: Draft DSMC memo: Final SUPPORT Trial Review
Date: Wednesday, November 04, 2009 4:08:29 PM
Attachments: DSMC Final Protocol Review Draft Memo.doc

Dear all,

Please find attached comments from the NICHD NRN DSMC based on their final review of the SUPPORT Trial. Please understand that this is a draft subject to revision when we share the final minutes with the DSMC.

Thanks,
Kris

Kris Zaterka-Baxter
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3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
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RTP, NC 27709 USA

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RTI INTERNATIONAL | **Memorandum**

November 4, 2009

SUPPORT Trial Final DSMC Review

TO: SUPPORT PI (co-PI)
NICHD

FROM: The Data Coordinating Center

SUBJECT: Final DSMC Protocol Review

The NICHD NRN DSMC met on November 4, 2009 in Rockville, MD to discuss the final planned interim analyses the *SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial).* Their recommendations and comments are below:

1. The DSMC agreed it was our obligation to share stratified mortality data from the oxygen saturation arm of the SUPPORT trial with DSMCs monitoring the safety data for other similarly conducted international trials without waiting for the primary papers to be published, so that those DSMCs can interpret the data. Additionally, we should share the oxygen saturation separation data so that the results can be put in context.
2. The DSMC requested additional information about the total number of protocol deviations and the total number of infants that had deviations.
3. The DSMC requested a 2x2 factorial distribution of mortality (death by cohort) and detailed reasons of death for those infants listed in the 'other' death category.
4. The DSMC requested that the DCC statistically test whether the separation in the saturation arms is statistically significant.
5. The DSMC has requested an additional review of the complete 18-22 month Follow Up data when available.

cc. Rose Higgins, MD

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT!
Date: Wednesday, November 04, 2009 2:31:31 PM
Attachments: info to share.doc

Would something like this work? Do you want this shared with the subcommittee/steering committee beforehand?

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 04, 2009 1:58 PM
To: Das, Abhik
Cc: Gantz, Marie; Zaterka-Baxter, Kristin
Subject: SUPPORT!

Abhik
Could you get us a brief summary of the information to be shared with the other dsmc's today so the NIH Director can review??

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Selected Information from

The Fourth Data Safety and Monitoring Committee Report for The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

CONFIDENTIAL

November 4, 2009

Prepared by the NICHD Neonatal Research Network Data Center at RTI International, Research Triangle Park, NC

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A. Methods and Procedures

Study Design

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested are:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant no longer requires ventilatory support or oxygen.

The oxygen saturation monitoring portion of the study is designed to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters that are calibrated to provide actual SpO2 values when the SpO2 is < 85% and > 95%. This methodology provides clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Primary Hypotheses

1) Relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks postmenstrual age (PMA).

2) Relative to infants managed with a higher SpO2 range, the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

Secondary Hypotheses

Use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decrease in mortality or neurodevelopmental impairment (NDI) at 18-22 months corrected age
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decrease in the percentage of infants who receive postnatal steroids for BPD
- A decreased incidence of BPD at 36 weeks PMA
- A decreased incidence of threshold ROP and/or the need for surgical intervention
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of intraventricular hemorrhage (IVH) and severe IVH
- A decreased incidence of periventricular leukomalacia (PVL)
- A decreased incidence of NDI at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up

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Study Population

Study subjects are infants of 24 0/7 to 27 6/7 weeks gestational age (GA) at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) are enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. There are 2 randomization strata, infants of 24 0/7 to 25 6/7 weeks GA, and infants of 26 0/7-27 6/7 weeks GA by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study is not powered to detect outcome differences between strata.

Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

Sampling Recruitment and Screening Procedures

Infants are recruited for this study by approaching parent(s) at the time of hospital admission when there is a perceived risk of premature delivery at 27 6/7ths weeks or less.

Sample Size

The required sample size for this trial was determined to be 1,310 to ensure 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. These results were based on observed prevalence of these outcomes in the Network Generic Data Base (GDB, a registry of all <1500 g births in the Network), and corrected for two primary outcomes (assumed significance level of 2%), for a clustering effect because of multiples being randomized to the same treatment, as well as for attrition. Note that this sample size is not sufficient to permit detection of interaction effects between the two treatments with reasonable power.

Randomization

Randomization is stratified by study site and gestational age group, occurs prior to delivery for consented deliveries, and is performed by utilizing specially prepared double-sealed envelopes. Deliveries are randomized as a unit, thus multiples, twins, triplets etc are randomized to the same arm of the trial. Appropriate sample size adjustments have been made to account for this clustering effect.

Study Intervention

The intervention begins after birth when the infant is given to the resuscitation team. The conduct of the resuscitation follows usual guidelines, and once stabilized, all Control infants in the Ventilation arm receive prophylactic/early surfactant (within 1 hour of age) whereas all

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Treatment infants are placed on CPAP/PEEP following stabilization and intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment is performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission. There are two ranges of SpO2 utilized during this trial. The Low target range is 85% to 89% and the High target range is 91% to 95%. The altered Pulse Oximeters (PO) display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO reads 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO displays 88% when the actual SpO2 is 91% and indicates 92% when the actual SpO2 is approximately 95%.

Interim Monitoring Plan

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion using interim monitoring boundaries. Efficacy is measured at approximately 25%, 50%, 75%, and 100% of outcome assessment. Primary outcomes are analyzed at these time points by statistically adjusting for familial clustering and stratification by gestational age stratum and center. To control for the inflation of Type I error associated with sequential testing, O'Brien-Fleming[1] boundaries are calculated using a Lan-DeMets[2] spending function. Safety is monitored at these time points as well using Pocock[3] boundaries for adverse event monitoring.

B. Results

Enrollment

This is the final planned DSMC look at 100% of the primary outcome data for the SUPPORT Trial. As of February 2009, 1,316 infants have been enrolled in SUPPORT, exceeding the total expected enrollment of 1,310.

~~**Table 1.a** displays information related to enrollment.~~

Category		Number	Percent
~~Screened*~~		~~3547~~	~~100%~~
~~Eligible~~		~~3186~~	~~90%~~
~~Consented~~		~~1384~~	~~39%~~
~~Randomized~~	~~% of Screened~~	~~1316~~	~~37%~~
	~~% of Eligible~~		~~41%~~
	~~% of Consented~~		~~95%~~
~~**Eligible – Not randomized**~~			
~~Infants~~		~~1870~~	~~100%~~
~~Reason – Parent unavailable~~		~~344~~	~~18.4 %~~
~~Reason – Parent refusal~~		~~748~~	~~40.0 %~~
~~Reason – Consent not requested~~		~~699~~	~~37.4 %~~
~~Reason – Other~~		~~79~~	~~4.2%~~

~~**Table 1.a** Enrollment Information Through February 2009~~
~~*Excludes infants who did not qualify for the NRN Generic Database~~

~~**Table 1.b** compares characteristics of eligible infants who were and were not~~

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randomized to the SUPPORT Trial. There are some statistically significant, though otherwise not dramatic, differences between these two groups. Note that antenatal steroid use is highly confounded by site in the Neonatal Network.

Characteristic	Randomized (N=1316)	Not randomized (N=1828)	p-value
Infant Characteristics			
GA: 24-25 weeks	43% (565/1316)	46% (846/1828)	0.0627
Birth Weight (grams)	830.1 ± 193.2	812.9 ± 191.5	0.0134
Small for gestational age	7% (96/1316)	8% (146/1827)	0.4700
Gender: Male	54% (712/1316)	52% (945/1828)	0.1823
Maternal/Delivery Characteristics			
Ethnicity: Hispanic	20% (259/1315)	17% (306/1827)	0.0338
Race: White	58% (754/1301)	54% (982/1804)	0.0512
Race: Black	39% (503/1301)	40% (726/1804)	0.3740
Multiple birth	26% (337/1316)	22% (410/1828)	0.0388
C-section	67% (883/1316)	69% (1261/1828	0.2628
Maternal age	27.1 ± 6.4	27.2 ± 6.6	0.8194
Parity	2.3 ± 1.5	2.2 ± 1.5	0.5170
Insurance: Medicaid	53% (694/1298)	47% (846/1797)	0.0005
Preeclampsia/eclampsia/ hypertension	25% (327/1316)	24% (433/1826)	0.4636
Antenatal steroids (any)	96% (1265/1315	86% (1575/1822	<0.0001
Antenatal steroids (complete course prior to delivery)	72% (939/1309)	50% (915/1813)	<0.0001

Table 1.b Characteristics of Eligible Infants Randomized and Not Randomized to SUPPORT
*42 infants were excluded from the table because they were born outside the 24-27 wk window or were missing data.

Baseline Characteristics

Table 2 compares selected characteristics of infants enrolled in the two arms of the study. There are no statistically significant differences between infants enrolled in the two treatments for either arm.

Treatment Compliance in Oxygen Saturation Arm

In the oxygen saturation arm, target saturation ranges are 85-89% and 91-95% for the Low and High SpO2 arms, respectively. **Table 3.a**| shows the percent of time infants on supplemental oxygen spent in various SpO2 ranges. Supplemental oxygen is defined as

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FiO2>.21 during the first 14 days of life (FiO2 is reported every two hours) or as documented oxygen use from day of life 15 through 36 weeks (oxygen use is recorded every 6 hours).

~~**Table 2** Infant Characteristics for Ventilation and Oxygen Saturation Arms~~

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Time on supplemental oxygen	Oxygen saturation arm	Percent in narrow target (85-92 Display)	Percent <84	Percent 84-96	Percent >96
Days of life 1-14	Low SpO2	19.7	11.8	76.2	12.0
	High SpO2	49.3	6.3	79.5	14.2
Day 15 to 36 wks	Low SpO2	15.5	15.4	67.1	17.6
	High SpO2	37.0	10.5	67.7	21.8

Table 3.a~~l~~ Distribution of Time in SpO2 Display Ranges while on Supplemental Oxygen

Separation in Oxygen Saturation Arm **Table 3.b~~ll~~** and **Figure ~~1~~** address treatment separation in the Oxygen Saturation arm of the SUPPORT Trial. **Table 3.b~~ll~~** shows the amount of time infants in each treatment group spend in room air. Only data from March 2006 to the present are included in Table 3.b, because since that time supplemental oxygen use has been recorded every two hours for day of life (DOL) 1-14 and every 6 hours thereafter. These data indicate some separation between the two treatment groups.

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	DOL 1-14		DOL 15+	
	High SpO2	Low SpO2	High SpO2	Low SpO2
Hours in room air (hours in thousands)	35% (57/162)	46% (71/157)	35% (213/600)	46% (254/552)

Table 3.b~~ll~~ Percent of Time Spent in Room Air Since March 2006, by Treatment and Day of Life

Figure ~~1~~ shows the distribution of SpO2 values during time spent on supplemental oxygen for infants in the Low and High SpO2 target groups through 36 weeks PMA. There is modest separation between the groups, along with substantial overlap. The area under the overlapping portions of the curves is 85%. Thus, 15% of the area under each curve does not overlap the other.

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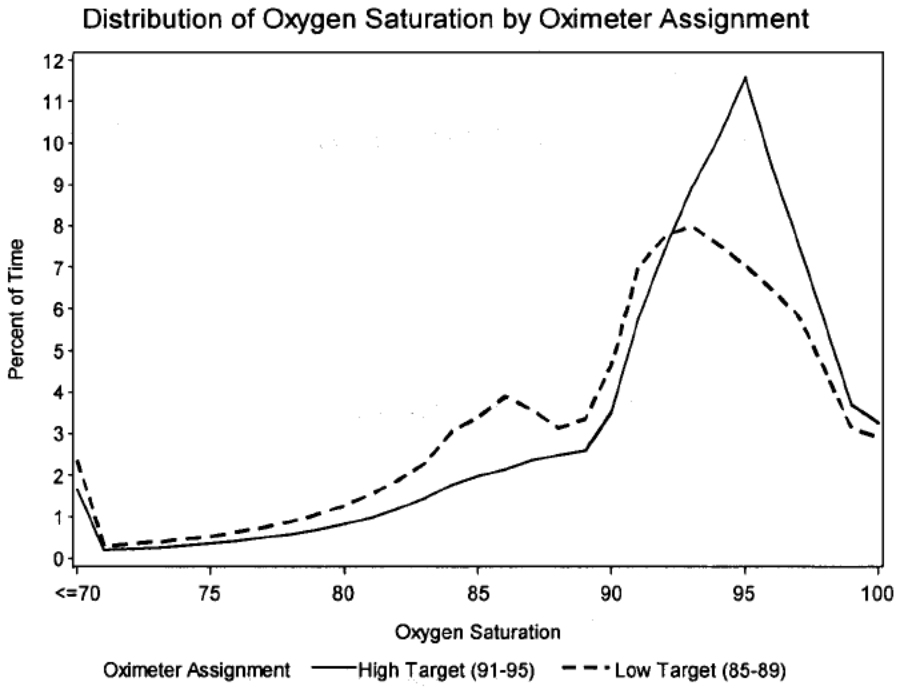

Figure 1 Percent of Time Spent at Each SpO2 Value for Infants in Low and High Target Groups (Includes only time on supplemental oxygen through 36 weeks PMA)

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Primary Outcomes

Tables 4.a and **4.b** compare the two primary outcomes for the ventilation and oxygen saturation arms. All enrolled infants had a known outcome for survival without BPD at 36 weeks, while 1,221 infants had a known outcome for survival without severe ROP (93% of total enrollment). P-values for testing for treatment differences are adjusted for familial clustering and for stratification by gestational age group and center.

[illegible]	[illegible] (N=663)	[illegible] (N=653)	Adjusted p-value
Survival without BPD (Physiologic Definition) at 36 weeks	52% (346/663)	49% (320/653)	0.33423039
Survival without BPD (Supplemental Oxygen) at 36 weeks	51% (3401/663)	46% (300/653)	0.06990719
Survival without severe ROP	72% (444/620)	68% (408/601)	0.12100971

Table 4.a Primary Outcomes for Ventilation Arm

Primary Outcome	[illegible] (N=654)	[illegible] (N=662)	Adjusted p-value
Survival without BPD (Physiologic Definition) at 36 weeks	51% (335/654)	50% (331/662)	0.94328988
Survival without BPD (Supplemental Oxygen) at 36 weeks	52% (3378/654)	46% (303/662)	0.07200754
Survival without severe ROP	72% (434/605)	68% (418/616)	0.19172050

Table 4.b Primary Outcomes for Oxygen Saturation Arm

Secondary Outcomes

Table 5.a shows selected secondary outcomes, by treatment. Tests between treatment groups were adjusted for stratification by center and gestational age and for familial clustering. Percentages and means (± standard error) for which there is a significant difference between treatments (adjusted p<0.05) are bolded. Aside from certain expected differences because of the nature of the interventions, the ventilation arm has suggestive trends in favor of CPAP for postnatal steroids for BPD (adjusted p=0.0005), and in favor of Surfactant for pneumothoraces and any grade of IVH (adjusted p-values of 0.0786 and 0.0265, respectively). Aside from expected differences due to treatments in the oxygen saturation arm, there were trends in favor of Low SpO2 for BPD by the supplemental oxygen definition (adjusted p=0.00170020), severe ROP in one or both eyes (adjusted p=0.0001), and days on supplemental oxygen (adjusted p=0.0002) among survivors.

At the 18 month follow-up visit, there was a trend in favor of Surfactant for NDI among survivors (adjusted p-value=0.0554). However, neither the ventilation nor oxygen saturation arm showed a significant difference between groups for the composite outcome of NDI or death.

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Characteristic	Ventilation Arm		Oxygen Saturation Arm	
	CPAP (N=663)	Surfactant (N=653)	Lower SpO2 (N=664)	Higher SpO2 (N=662)
Hospital Outcomes				
Intubation in the DR	**34% (227/660)**	**93% (609/652)**	62% (404/652)	65% (432/660)
Intubation (1st time) in the NICU	**42% (280/661)**	**6% (40/648)**	25% (164/651)	24% (156/658)
Intubation in the DR or NICU	**77% (508/661)**	**100% (649/652)**	87% (568/652)	89% (589/661)
Surfactant use in the DR	**14% (93/660)**	**51% (335/652)**	31% (201/652)	34% (227/660)
Surfactant use in the NICU	**61% (403/662)**	**72% (466/646)**	64% (417/651)	69% (451/657)
Surfactant in the DR or NICU	**67% (443/660)**	**99% (646/653)**	81% (531/653)	85% (558/660)
Air leak in first 14 days*	7% (45/663)	7% (48/653)	8% (51/654)	6% (42/662)
Air leak (pneumothorax)	8% (54/663)	6% (36/653)	7% (47/654)	6% (43/662)
Postnatal steroids for BPD	**7% (47/649)**	**13% (83/631)**	10% (61/636)	11% (69/644)
BPD (Physiologic definition)	39% (223/569)	41% (219/539)	38% (205/540)	42% (237/568)
BPD (Supplemental oxygen)	40% (229/569)	44% (239/539)	**38% (203/540)**	**47% (265/568)**
ROP in one or both eyes	14% (70/517)	14% (68/480)	**9% (43/483)**	**18% (95/514)**
NEC	13% (83/654)	10% (63/636)	12% (76/641)	11% (70/649)
Any IVH (any grade)	**32% (204/642)**	**26% (164/628)**	29% (184/630)	29% (184/640)
IVH grade 3 or 4	14% (92/642)	11% (72/628)	13% (83/630)	13% (81/640)
PVL	4% (28/643)	4% (26/629)	4% (24/631)	5% (30/641)
Respiratory support for infants who survived to status (discharge, transfer, hospitalized at 120 days)				
Average days on mechanical ventilation (CV, HFV)	**24.8 ± 1.0**	**27.7 ± 1.1**	25.5 ± 1.1	26.9 ± 1.0
Average days on non invasive support (nSIMV, CPAP)	20.7 ± 0.7	20.5 ± 0.7	20.3 ± 0.7	20.8 ± 0.7
Average days on supplemental O_2	62.2 ± 1.6	65.3 ± 1.6	**59.8 ± 1.6**	**67.4 ± 1.5**
Average percent of time with pulse oximetry values > 90% through 36 weeks PMA	70.1 ± 0.7	68.7 ± 0.7	63.1 ± 0.6	75.8 ± 0.6
Neurodevelopmental outcomes at 18-22 months of age				
NDI or death	36% (158/442)	37% (163/438)	37% (168/449)	35% (153/431)
NDI among survivors	13% (41/325)	8% (25/300)	9% (29/310)	12% (37/315)
Cerebral palsy (mild, moderate or severe) among survivors	10% (33/334)	6% (18/304)	7% (22/317)	9% (29/321)
Blindness (in at least 1 eye) among survivors	1% (4/334)	2% (6/304)	1% (3/317)	2% (7/321)

Table 5.a Secondary Outcomes, by Treatment

*Air leaks collected since 10/15/07 include PIE and pneumopericardium in addition to pneumothorax

Tables 5.b, 5.c and 5.d address safety-related questions pertaining to IVH and air leaks. **Table 5.b** shows the frequency of air leaks in the first 14 days of life (data collected since October 15, 2007, include PIE and pneumopericardium in addition to pneumothorax) and IVH in the SUPPORT Trial. There is some evidence of an association, with any IVH and severe IVH (grades III-IV) occurring more frequently in cases of air leak (unadjusted chi-square p-values both<0.0001). **Table 5.c** shows the relationship between pneumothorax and IVH. Unadjusted chi-square p-values for the independence of pneumothorax and any IVH or severe IVH were both <0.0001. **Table 5.d** shows the distribution of the number of hours between delivery and surfactant receipt for infants with and without pneumothorax.

Category	Percent with any IVH	Percent with IVH grade III-IV

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Category	Percent with any IVH	Percent with IVH grade III-IV
Air leak = Yes	50% (43/86)	34% (29/86)
Air leak = No	27% (325/1184)	11% (135/1184)
Total	29% (368/1270)	13% (164/1270)

Table 5.b Percent of Infants with IVH, by Air Leak Category

Category	Percent with any IVH	Percent with IVH grade III-IV
Pneumothorax = Yes	48% (41/85)	32% (27/85)
Pneumothorax = No	28% (327/1185)	12% (137/1185)
Total	29% (368/1270)	13% (164/1270)

Table 5.c Percent of Infants with IVH, by Pneumothorax Category

Category	N	Mean ± StdDev	25th Percentile	Median	75th Percentile	90 Percentile
Pneumothorax = Yes	88	7.4 ± 14.9	0.4	0.7	8.9	24.1
Pneumothorax = No	995	3.0 ± 9.1	0.3	0.6	1.3	5.7

Table 5.d Number of Hours Between Birth and Receipt of Surfactant

Note: 231 infants without pneumothorax and 2 with pneumothorax are not included in this table because the infant did not receive surfactant or timing of surfactant was unknown

Death and other Adverse Events Mortality Information

Deaths **Tables 6.a** and **6.bIII** show the percent of infants in each treatment group who died during the course of the SUPPORT Trial. The table also displays adjusted p-values for statistical tests comparing the percent of infants who died in each level of the two treatment factors. The tests are adjusted for familial clustering due to multiple births and for stratification by center and gestational age group. There is a statistically significant difference in the death rate between treatments in the oxygen saturation arm, with higher mortality in the low SpO2 arm.

Outcome	Ventilation Arm		Adjusted P-value
Death	16% (109/663)	20% (128/653)	0.1259

Table 6.a Death in the Ventilation Arm

Outcome	Oxygen Saturation Arm		Adjusted P-value
	Low SpO2 (N=654)	High SpO2 (N=654)	
Death	20% (130/654)	16% (107/662)	0.0412

Table 6.bIII Death in the Oxygen Saturation Arm

Gestational age was a significant predictor of death in the tests presented in Table 6.a and 6.bIII ($p<0.0001$). **Tables 6.c** and **6.dIV** presents the mortality information by gestational age stratum. Note that the 26-27 week gestational age stratum includes three infants born at 28 weeks gestational age. There is a significant difference in deaths between the CPAP and Surfactant groups for infants in the 24-25 week gestational age stratum.

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~~GA 24-25 weeks (N=565)~~	~~24% (68/285)~~	~~32% (90/280)~~	~~0.0 335~~
~~GA 26-27 weeks (N=751)~~	~~11% (41/378)~~	~~10% (38/373)~~	~~0.7 966~~

~~**Table 6.c** Death in the Ventilation Arm by Gestational Age Group~~

Gestational Age Strata	Oxygen Saturation Arm: Low SpO2	High SpO2	Adjusted P-value
GA 24-25 weeks (N=565)	31% (85/276)	25% (73/289)	0.1225
GA 26-27 weeks (N=751)	12% (45/378)	9% (34/373)	0.1811

Table ~~6.d~~IV Death in the Oxygen Saturation Arm by Gestational Age Group

Cause of Death **Tables ~~6.e~~ and ~~6.f~~V** lists causes of death by treatment ~~arm~~ and gestational age group to address safety concerns regarding RDS and other factors contributing to mortality.

Cause of Death	Low SpO2 24-25 wks (N=85)	Low SpO2 26-27 wks (N=45)	High SpO2 24-25 wks (N=73)	High SpO2 26-27 wks (N=34)
RDS	27% (23/85)	18% (8/45)	29% (21/73)	29% (10/34)
BPD	9% (8/85)	13% (6/45)	12% (9/73)	3% (1/34)
Infection	19% (16/85)	20% (9/45)	18% (13/73)	24% (8/34)
NEC	20% (17/85)	13% (6/45)	12% (9/73)	15% (5/34)
CNS Insult	12% (10/85)	4% (2/45)	8% (6/73)	9% (3/34)
Immaturity	6% (5/85)	4% (2/45)	4% (3/73)	0% (0/34)
Other	7% (6/85)	27% (12/45)	16% (12/73)	21% (7/34)

Table V Cause of Death, by Oxygen Saturation Treatment and GA at Birth

~~All Adverse Events Adverse events (AEs) in the first 14 days of life are recorded on a designated SUPPORT form. Later events are identified using other SUPPORT and Generic Database (GDB) forms. AEs monitored for the SUPPORT Trial in addition to death include:~~

- ~~Air leak (data collected since October 15, 2007, include PIE and pneumopericardium in addition to pneumothorax)~~
- ~~Need for chest compressions or epinephrine in the delivery room or NICU~~
- ~~Severe IVH (Grades 3-4, Papile)~~
- ~~Pulmonary hemorrhage~~
- ~~Nasal breakdown requiring discontinuation of nasal prongs~~

Contributing	CPAP	Surfactant

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Cause of Death	24-25 wks (N=68)	26-27 wks (N=41)	24-25 wks (N=90)	26-27 wks (N=38)
RDS	19% (13/68)	22% (9/41)	34% (31/90)	24% (9/38)
BPD	15% (10/68)	5% (2/41)	8% (7/90)	13% (5/38)
Infection	21% (14/68)	29% (12/41)	17% (15/90)	13% (5/38)
NEC	15% (10/68)	10% (4/41)	18% (16/90)	18% (7/38)
CNS Insult	16% (11/68)	5% (2/41)	6% (5/90)	8% (3/38)
Immaturity	4% (3/68)	2% (1/41)	6% (5/90)	3% (1/38)
Other	10% (7/68)	27% (11/41)	12% (11/90)	21% (8/38)

Table 6.e Cause of Death, by Ventilation Treatment and GA at Birth

Cause of Death	Low SpO2 24-25 wks (N=85)	Low SpO2 26-27 wks (N=45)	High SpO2 24-25 wks (N=73)	High SpO2 26-27 wks (N=34)
RDS	27% (23/85)	18% (8/45)	29% (21/73)	29% (10/34)
BPD	9% (8/85)	13% (6/45)	12% (9/73)	3% (1/34)
Infection	19% (16/85)	20% (9/45)	18% (13/73)	24% (8/34)
NEC	20% (17/85)	13% (6/45)	12% (9/73)	15% (5/34)
CNS Insult	12% (10/85)	4% (2/45)	8% (6/73)	9% (3/34)
Immaturity	6% (5/85)	4% (2/45)	4% (3/73)	0% (0/34)
Other	7% (6/85)	27% (12/45)	16% (12/73)	21% (7/34)

Table 6.f Cause of Death, by Oxygen Saturation Treatment and GA at Birth

Table 6.g shows the overall percent of infants in each treatment group who had an AE, as well as the number of infants who experienced each individual type of event. There was not a significant difference between treatment groups in the overall percent of infants who had an AE in either the ventilation or oxygen saturation arm (p-values 0.9393 and 0.0726, respectively, adjusted for familial clustering due to multiple births and for stratification by center and gestational age group). Neither arm of the study had a significant difference between treatment groups in the overall percent of infants who had an AE when viewed by GA group.

The only individual events showing a trend for differences between treatments in adjusted tests were nasal breakdown (ventilation arm p-value 0.0896) and, as seen earlier, death in the oxygen saturation arm (p-value=0.0412).

Characteristic	Ventilation Arm		Oxygen Saturation Arm	
	CPAP (N=663)	Surfactant (N=653)	Low SpO2 (N=654)	High SpO2 (N=662)
Air leak in the first 14 days	7% (45/663)	7% (48/653)	8% (51/654)	6% (42/662)
Chest compressions/drugs in DR	5% (36/660)	7% (46/653)	6% (41/651)	6% (41/662)
IVH grade 3 or 4	14% (92/642)	11% (72/628)	13% (83/630)	13% (81/640)

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Characteristic	Ventilation Arm		Oxygen Saturation Arm	
	CPAP/NIPPV (N=663)	Ventilation (N=653)	Low SpO2 (N=654)	High SpO2 (N=662)
Pulmonary hemorrhage	5% (33/654)	7% (45/636)	7% (44/641)	5% (34/649)
Nasal breakdown in first 14 days	3% (17/663)	1% (8/653)	2% (14/654)	2% (11/662)
Death	16% (109/663)	20% (128/653)	20% (130/654)	16% (107/662)
Other AE in first 14 days	5% (33/663)	5% (33/653)	5% (33/654)	5% (33/662)
All adverse events combined	37% (247/663)	37% (239/653)	39% (255/654)	35% (231/662)

Table 6.g Adverse Events by Treatment Arm

Historic AE Rates in the Neonatal Research Network - In order to provide comparable prevalence rates for the AEs experienced by this severely ill population, **Table 6.h** displays rates of AEs among infants born at Neonatal Research Network (NRN) centers between 2002 and 2004. The table shows the percent of infants experiencing AEs for all centers combined, as well as ranges across the individual centers. Death and overall AE rates in the SUPPORT Trial appear to be comparable to, and fall within the plausible ranges of such events in the NRN population.

Adverse Event	22 to 28 Weeks Gestational Age		23 to 27 Weeks Gestational Age		All Infants 22 to 27 Weeks Gestational Age	
	Percent	Range	Percent	Range	Percent	Range
Air leak (pneumothorax)	11.0	2.9 - 20.6	6.1	1.1 - 13.0	8.2	1.9 - 16.1
Chest compressions/ epinephrine in the DR	13.9	2.8 - 42.1	9.1	3.2 - 23.2	11.2	3.2 - 31.8
Severe IVH (grades III-IV)	24.2	14.0 - 38.9	11.7	2.3 - 20.8	16.9	8.4 - 26.4
Pulmonary hemorrhage	12.3	2.5 - 32.0	6.5	1.1 - 26.9	9.0	3.4 - 29.3
Death	35.5	19.9 - 66.1	13.3	4.4 - 26.8	23.1	12.1 - 46.4
Any AE listed above	57.4	42.0 - 78.6	31.5	20.8 - 53.6	42.9	23.3 - 66.1

Table 6.h Adverse Event Rates in the NRN: Births in 2002-2004

Necrotizing Enterocolitis (NEC) and Patent Ductus Arteriosus (PDA) - In December 2007, a Hot Topics presentation regarding oxygen saturation prompted concern that NEC and/or PDA rates might increase when infants were maintained in certain saturation ranges. Thus, monitoring for those two adverse events was added to the safety monitoring routine for SUPPORT.

Table 6.i and shows the percent of infants in the two treatment groups of the oxygen saturation arm who had NEC or PDA, as well as p-values for statistical tests comparing the percent of infants experiencing those events in the two treatment groups. The tests are adjusted for familial clustering due to multiple births and for stratification by center and gestational age group.

Outcome	Oxygen Saturation Arm		Adjusted p-value
	Low SpO2 (N=654)	High SpO2 (N=662)	
NEC	12% (76/641)	11% (70/649)	0.5076

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PDA	48% (307/641)	50% (324/648)	0.4320

Table 6.i Tests for Differences Between Treatments in the Oxygen Saturation Arm

NEC and PDA Rates in the Generic Database **Table 6.j** displays rates of NEC and PDA among infants born at Neonatal Research Network (NRN) centers between 2002 and 2004. The table shows the percent of infants with NEC and PDA for all centers combined, as well as ranges across the individual centers. The overall rates of NEC and PDA in the SUPPORT Trial are comparable to the historic GDB rate.

NEC	12.3	5.0 – 25.9	9.7	3.9 – 19.4	10.8	5.1 – 22.3
PDA	57.1	37.8 – 75.3	44.1	18.2 – 68.9	49.7	28.1 – 71.7

Table 6.j NEC and PDA Rates in the NRN: Births in 2002-2004

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Protocol Deviations

Table 7 summarizes protocol deviations for all enrolled infants. A total of 388 protocol deviations were reported by the centers or identified using study forms. Most of these were related to failure to administer surfactant in the first hour if required by protocol (infants in the CPAP arm are required to receive surfactant if intubated for resuscitation) or failure to use study oximeter at times required by protocol. Note that in 70% of the cases where surfactant was not given in the first hour it was still administered within two hours of delivery, and in 94% of cases it was administered within 3 hours of birth. Except for certain expected differences due the nature of the interventions, the distribution of the deviations does not appear substantially skewed between the two groups in either arm.

	Initial Therapy		Oxygen Saturation Arm	
	CPAP	Surfactant	Low Sat	High Sat
CPAP not initiated if required by protocol	5	1	2	4
Surfactant not given in the first hour (if required by protocol)	45	36	43	38
Oximeter not started within two hours of NICU admission	15	16	13	18
Infant received incorrect treatment	15	11	15	11
Failure to use study oximeter at times required by protocol	55	57	57	55
Non-study oximeter used at same time as study oximeter	8	7	9	6
Mechanical ventilation initiated for other than study criteria	2	0	1	1
NSIMV initiated in infant not previously intubated	10	0	3	7
Extubation (excluding unplanned) for other than study criteria	2	10	8	4
Failure to extubate infant if all criteria met	8	4	6	6
Infant intubated without meeting study criteria	2	0	1	1
Infant received postnatal steroids in first 21 days of life	15	19	20	14
Randomization/consent errors	14	18	15	17
Other	6	7	5	8
Total	**202**	**186**	**198**	**190**

Table 7. Protocol Deviations

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Abhik Das; "Gantz, Marie"
Subject: Re: manuscripts
Date: Wednesday, November 04, 2009 1:02:27 PM
Attachments: SUPPORT CPAP vs Surf Nov 3 09 doc for circ.docx
Tables Nov 3 09.docx

Hi Rose
Here is the SUPPORT CPAP Surf paper with Tables for circulation
Neil
On 11/4/09 9:33 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi,
Can you send me the updated versions of the manuscripts for distribution to the SC members and co-authors by Monday?? Have you received input from the subcommittee members?

Thanks
Rose

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven minimal ventilator strategy. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, ~~(p<.001)~~ (p<0.001).

Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

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Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

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There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] The surfactant trials preceeded widespread use of antenatal corticosteroids to promote lung maturation. Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses~~6~~, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a protocol-directed ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven minimal ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center without known malformations, for whom a decision had been made to provide full resuscitation, and parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was to be performed only for the standard NRP indications (need ref) including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was allowed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour,

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an arterial $PaCO_2$ > 65 torr documented on a single blood gas within one hour of intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standardpractice.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 ≥88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard practice.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

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Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1617]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed

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as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. (Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery

Results:

There were 1316 infants enrolled in this trial from Feb 2005 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more

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epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, $p=0.060$) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, $p=0.03$, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.019$). There were no significant

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differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation (post hoc analysis)

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[15,14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven minimal ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven minimal ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a higher threshold approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to have a higher threshold for intubation.

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Our study has demonstrated that early CPAP and protocol driven mimimal ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to

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evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth, ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven minimal ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence-based alternative to intubation and surfactant.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	03681
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0978

Table 2. Delivery Room interventions

Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	<0.0001*
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation	33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.0225*

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9630
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	100.4 ± 42.9	101.4 ± 41.6	0.7047
Days on supplemental oxygen (survivors only)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors only)	20.0 ± 23.9	23.2 ± 26.2	0.0331
Discharge on oxygen	22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days	55% (362/655)	49% (318/652)	0.0188
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC	13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery	11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4	14% (92/642)	11% (72/628)	0.1279
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0005

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/280)	0.5217
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.7 ± 47.9	119.2 ± 40.5	0.7394
Days on supplemental oxygen (survivors only)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors only)	33.1 ± 27.3	37.5 ± 29.0	0.1138
Discharge on oxygen	32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days	34% (97/283)	26% (74/280)	0.0429*
Any air leak in first 14 days	8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC	15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery	16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4	20% (54/273)	17% (45/265)	0.4022
Postnatal steroids for BPD	13% (36/276)	20% (54/264)	0.0209*

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SC Call
Date: Wednesday, November 04, 2009 11:16:57 AM

I am OK with that- Use the ones that you have modified
Neil

On 11/4/09 5:34 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

I propose we send the manuscripts to the PI's and the co-authors.

Rose

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, November 03, 2009 5:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Webb, Robin E.
Subject: RE: SC Call

Are we (the non-subcommittee members) going to get a copy of the outcome data to review before the call? It's a lot to digest and I think the steering committee discussion was suboptimal because people hadn't had a chance to review the data beforehand.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Tuesday, November 03, 2009 3:46 PM
To: Webb, Robin E.; mca113@northwestern.edu; Walsh, Michele; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; [SCRN] Stoll, Barbara; kurt.schibler@cchmc.org; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; Laptook, Abbot; vanmeurs@leland.stanford.edu; wcarlo@peds.uab.edu; Kennedy, Kathleen A; goldb008@mc.duke.edu; Ifrantz@tufts-nemc.org; Roger.Faix@hsc.utah.edu; Kristi Watterberg; edward-bell@uiowa.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu
Cc: StWilliams@peds.uab.edu; gonza025@mc.duke.edu; bvecchio@careNE.org; lmoore@med.wayne.edu; jwaidne@emory.edu; Rose, Joyce; archerst@mail.nih.gov; Cunningham, Meg; Zaterka-Baxter, Kristin; Irene, Amanda; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; Cunningham, Meg; Smith, Nancy M
Subject: SC Call

The call to discuss the final versions of the two papers for the SUPPORT study has been scheduled as detailed below. We picked the time that worked for the most number of people. if you are unable to make this time, please have your co-PI or coordinator join.

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Monday, 11/16
4:00pm ET

Dial:
Within the USA
866-675-(b) (6)
or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Cc: "kzaterka@rti.org"
Subject: Re: SUPPORT DSMC
Date: Tuesday, November 03, 2009 2:35:14 PM

Hi Rose
I am available at 619 405 (b) (6)
Or my office at 619 543 3285
Neil

On 11/3/09 11:14 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> Agree-Neil can you send us a number in case we need to reach you?
>
> ----- Original Message -----
> From: Das, Abhik <adas@rti.org>
> To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>
> Sent: Tue Nov 03 14:12:39 2009
Subject: RE: SUPPORT DSMC
>
> I think you can just be available; it is from 10-11:30 am EST.
>
> Thanks
>
> Abhik
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, November 03, 2009 2:04 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Das, Abhik
> Subject: SUPPORT DSMC
>
> Rose
> Am I supposed to be on the DSMC Call or just available??
> Thanks
> Neil

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Urgent info request: CTSA
Date: Tuesday, November 03, 2009 12:45:40 PM

Hi Rose:

University of Rochester:
For the SUPPORT study: no CTSA

Our SUPPORT participation was before the University converted to the CTSA on 9/30/2006. Therefore, the (former) CRC tells me that the appropriate citation is:

"This publication was made possible by Grant Number 5 MO1 RR00044 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH."

I realize you will probably not use all of that wording.
Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 9:23 AM
To: 'Luc.Brion@UTSouthwestern.edu'; 'rohls@unm.edu'; 'aaf2@po.cwru.edu'; 'adas@rti.org'; 'alaptook@WIHRI.org'; 'ambal@uab.edu'; 'Bradley.yoder@hsc.utah.edu'; 'bpoindex@iupui.edu'; 'wcarlo@peds.uab.edu'; 'cotte010@mc.duke.edu'; 'dwallace@rti.org'; 'edward-bell@uiowa.edu'; 'edward.donovan@cchmc.org'; 'richard.ehrenkranz@yale.edu'; 'ifrantz@tuftsmedicalcenter.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kwatterberg@salud.unm.edu'; 'kurt.schibler@cchmc.org'; 'mcw3@po.cwru.edu'; 'mcaplan@northshore.org'; 'william_oh@brown.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'poo@rti.org'; 'Roger.Faix@hsc.utah.edu'; 'goldb008@mc.duke.edu'; 'sshankar@med.wayne.edu'; 'dstevenson@stanford.edu'; 'barbara_stoll@oz.ped.emory.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'vanmeurs@leland.stanford.edu'; Phelps, Dale; 'nfiner@ucsd.edu'; 'moshea@wfubmc.edu'; 'sduara@miami.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'cunningham@rti.org'; 'kzaterka@rti.org'; 'petrie@rti.org'
Subject: Urgent info request: CTSA

Hi,
Please send me an email by November 3 indicating whether or not your site received CTSA support for the SUPPORT main trial. This information is essential for an accurate boilplate.

Thanks
Rose

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From: Das, Abhik
To: Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: Manuscript
Date: Monday, November 02, 2009 2:04:58 PM
Attachments: SUPPORT CPAP vs Surf Oct 31 09 adrev.docx
Oxygen Saturation Target 10 30 09 NF AD Rev.doc

I have appended my comments and suggested changes to Neil's edits. We also need to think about whether we want to harmonize the titles of the two papers in some manner. Also, in reviewing Wally's paper, I made some other changes to Neil's paper (also attached). Please use this version rather than the one I sent out earlier today.

Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, October 30, 2009 8:56 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Rich, Wade
Subject: RE: Manuscript

Hi Wally
Very nice, succinct. I removed one sentence that I think is redundant in the intro. Marie can you please add all the relevant p values and then we can send out to the Subcommittee
Thanks for a wonderful effort Wally
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, October 30, 2009 3:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; Das, Abhik
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology

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Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of California at San Diego, San Diego, CA; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University

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of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]Univresity of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center Floating Hospital for Children (GCRC M01 RR54, U10 HD53119) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Wade Rich, BSHS RRT.

University of Iowa Children's Hospital (CTSA UL1 RR24979, GCRC M01 RR59, U10 HD53109) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS.

University of Rochester Golisano Children's Hospital at Strong (GCRC M01 RR44, U10 HD40521) – Nirupama Laroira, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (GCRC M01 RR633, U10 HD40689) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (CTSA UL1 RR25764, GCRC M01 RR64, U10 HD53124) – Roger G. Faix, MD; Bradley A. Yoder, MD; Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University Baptist Medical Center Brenner Children's Hospital and Forsyth Medical Center (GCRC M01 RR7122, U10 HD40498) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Dan Gingras, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (CTSA UL1 RR24139, GCRC MO1 RR125, GCRC M01 RR6022, U10 HD27871) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Word count:

Abstract: 250

Manuscript: 3069

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to either CPAP initiated in the delivery room, and were subsequently treated using a protocol driven minimal ventilator strategy, ~~. Infants randomized~~ or, to surfactant, and were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001) ~~(p<0.001)~~.

Conclusions: The use of surfactant within 1 hour of birth and conventional mechanical ventilation in ELBW infants between 24 and 27 6/7ths weeks gestation at birth, compared to treatment with CPAP and

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a protocol driven minimal ventilator strategy, did not decrease the incidence of death or survival with BPD at 36 weeks. There was also no demonstrable increase in any adverse neonatal outcomes in infants treated with CPAP. The use of CPAP in such infants is thus an effective evidence based alternative to intubation and surfactant.

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Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent

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review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses46, and a reduction in death or the need for oxygen at

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28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. ~~We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.~~

Comment [AD1]: I think this can be deleted here because we say it in the Methods section.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also simultaneously randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven

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minimal ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained antenatally. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.-, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

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These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

~~Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.~~

Comment [AD2]: This is a repeat, and can be deleted.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks by an absolute difference of 10%.~~,~~ ~~(~~Our sample size calculations were based upon~~using~~ the NRN ~~occurrence~~ rate of death or survival with BPD of 67% ~~using~~ from the year 2000 data, a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age), and a conservative outcome rate of 50%.~~), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%.~~ Based on a historic intra-cluster correlation of 0.12 in this outcome (from analysis of 2000 NRN data), w~~W~~e further increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because ~~as~~ this introduced a clustering effect into the design.~~, and increased the sample sizes by a further~~We inflated the required sample size by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310~~2~~ infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

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Comment [AD3]: I think we need to be consistent in whether we frame the hypothesis as increased survival free of BPD or reduced death/BPD, and the tables should follow that approach.

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In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

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Statistical analyses: Intent~~ion~~-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided p~~P~~ value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock and ~~(~~O'Brien-Fleming~~)~~ boundaries were used to develop stopping rules for interim safety and efficacy monitoring respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

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Results:

There were 1316 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 (Figure 1). The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial ~~was continued~~resumed in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no statistically significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

Comment [AD4]: This would be the CONSORT flow diagram.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

There was no statistically significant difference in the primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age, between the treatment groups. A trend towards reduced death or BPD was however noted ~~was non-significantly reduced~~ for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, p=0.06~~0~~) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group

Comment [AD5]: I want to say this upfront just to satisfy the NEJM!

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overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,~~,~~ 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.0001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). There was a trend towards reduced incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] ~~was non- significantly reduced~~ in ~~in~~ the CPAP compared to the surfactant infants, ~~(~~23% vs 31%, RR=0.75(0,54, 1.05).

Strata Results: 24 – 25 weeks Gestation

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There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized, 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this stratuma.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, mean of 40.6 vs 47.1 days, p=0.01, and lesser days of mechanical ventilation, mean of 11.3 vs 14.9 days, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

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Our study differs from the recently reported COIN trial[~~15~~14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven minimal ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven minimal ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that the use of surfactant within 1 hour of birth and conventional mechanical ventilation in ELBW infants between 24 and 27 6/7ths weeks gestation at birth, compared to treatment with CPAP and a protocol driven minimal ventilator strategy, does not decrease the incidence of death or survival with BPD at 36 weeks. Our data indeed suggests that early CPAP ~~and protocol driven mimimal ventilator strategy when~~ compared with surfactant ~~given within 1 hour of birth was~~ is associated with a ~~reduction non-significant~~ decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a ~~very~~ substantial (and statistically significant) 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with trends

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towards reductions in BPD, ROP, -significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes -represents a substantial clinical benefit compared with the initial use of early surfactant~~,~~.

Comment [AD6]: I am worried that this statement will be perceived to be stronger than our data allow. After all, the reduced deaths are only in the 24-24 weekers.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of air leaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in air leaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of CPAP and a protocol driven minimal ventilator strategy, ~~surfactant within 1 hour of birth~~ ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with ~~CPAP and a protocol driven minimal ventilator strategy~~ surfactant within 1 hour of birth do

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not have a ~~non-significant~~ decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA. There is a strong trend towards reduced death or BPD in the CPAP group with no demonstrable increase in any adverse -neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

COMMENT ON TABLES: All tables need to have adjusted p values. Also, if we are presenting a table for the 24-25 weekers, we need to do the same for the 26-27 weekers.

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Randomized Trial of Higher Versus Lower Oxygen Saturation Targeting in Extremely Premature Infants

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death. ~~As part of the SUPPORT Trial, infants were also randomized to continuous positive airway pressure and a protocol-driven limited ventilator strategy or to surfactant and ventilation.~~

Comment [AD1]: I don't think we need this in the abstract itself.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; P = ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; P = 0.__) and was partially offset by a lower rate of threshold retinopathy (9 vs 18%; RR 0.51, 0.37, 0.71; P = ___).

Comment [AD2]: Both here and in the conclusion, we need to think about how to phrase this – can death be really offset by anything?! Perhaps we can say something like 'An observed benefit of less ROP in the lower sat group was negated by higher mortality in that group'.

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease the combined outcomes of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in

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threshold retinopathy. The increased mortality is of concern since~~as~~ lower saturation targeting is increasingly being advocated ~~as it has~~because of its short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. ~~Pulse oximetry has become the standard technique for continuous monitoring of oxygenation.~~ While data from these recent prospective observational and retrospective studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

Comment [A3]: Previously stated above

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses, and will be reported separately.

METHODS

The institutional review boards at all Neonatal Research Network (NRN) clinical centers and at ~~Research Triangle~~RTI International, the independent Data Coordinating Center for the NRN ~~(data center)~~, approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

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Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation, without a decision to forego resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) ~~with balancing blocks~~using permuted block randomization. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[20] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, -respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinicians, and not by the research staff. Reports of displayed data by

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~~treatment arm and~~ clinical center were provided quarterly for feedback on targeting performance. ~~For the ventilation part of this 2 by 2 factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy..~~

Comment [AD4]: Since this has already been covered in the Introduction, I don't think it needs to be repeated here.

Assessments

Research nurses recorded all data using standardized definitions laid out in the trial Manual of Operations. Data were collected until discharge except for retinopathy. Outcomes included only predefined clinical diagnoses and potential adverse events. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

Comment [AD5]: These 2 sentences seem a bit confusing and opaque to me; perhaps they need to be expanded upon, or deleted.

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

~~Follow-up at 18-22 months is being conducted.~~

Statistical analysis

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The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturation values between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. Our sample size calculations were based upon the NRN rate of death or threshold ROP of 50% from the year 2000 data and a conservative 2% level of significance (to account for a co-primary outcome of death or neurodevelopmental impairment at 18-22 months corrected age). Based on a historic intra-cluster correlation of 0.12 in this outcome (from analysis of 2000 NRN data), we further increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because this introduced a clustering effect into the design. We inflated the required sample size by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1310 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.~~To detect this difference, we planned to enroll 1310 infants for 80% power to detect a 10% difference in outcome assuming a baseline estimated rate of 50% of death/threshold retinopathy/surgery. This sample size estimate included an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. While these sample size calculations allowed for the testing of two co-primary outcomes for the two interventions (oxygen saturation~~

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~~targeting and protocol-driven, limited ventilator strategy) of this 2 by 2 factorial trial, the trial was not powered to determine an interaction between the interventions.~~

Comment [AD6]: I made this change so that this section reads almost the same for the 2 papers.

Intent~~ion~~-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the NRN data center. A two-sided p~~P~~ value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock and ~~(~~O'Brien-Fleming~~)~~ boundaries were used to develop stopping rules for interim safety and efficacy monitoring respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

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Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; pP=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; P=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was decreased in the lower oxygen saturation targeted group (9 vs 18%; CI 0.51, RR 0.37, 0.71; pP=0._____). Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test on oxygen at 36 weeks and the composite outcome of bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was substantial overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

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DISCUSSION

Comment [AD7]: As it is, this discussion is currently almost entirely focused on the mortality outcome. I think we need to add discussion on the ROP benefit and the tradeoff between death and ROP, and the treatment implications of this finding.

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies, and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, in a large multi-center randomized trial we found that even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

This trial was not powered for examining a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction among the outcomes evaluated. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Comment [AD8]: Was this written before we had the ROP outcomes? Lower sat certainly appears to reduce ROP, specially in the more immature babies.

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Restriction of oxygenation in previous randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[23] At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	17/605 (28)	198.616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.6)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.9, 1.1)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.8, 1.4)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.8, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (7)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

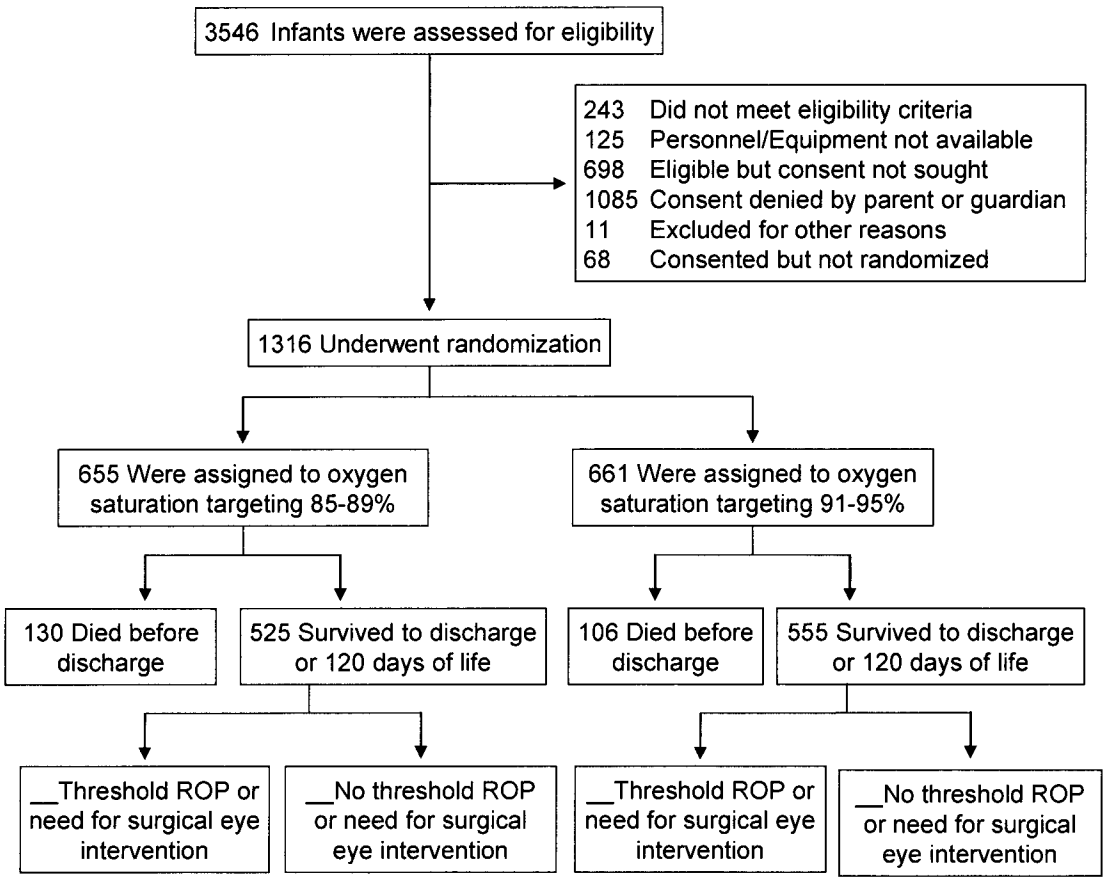

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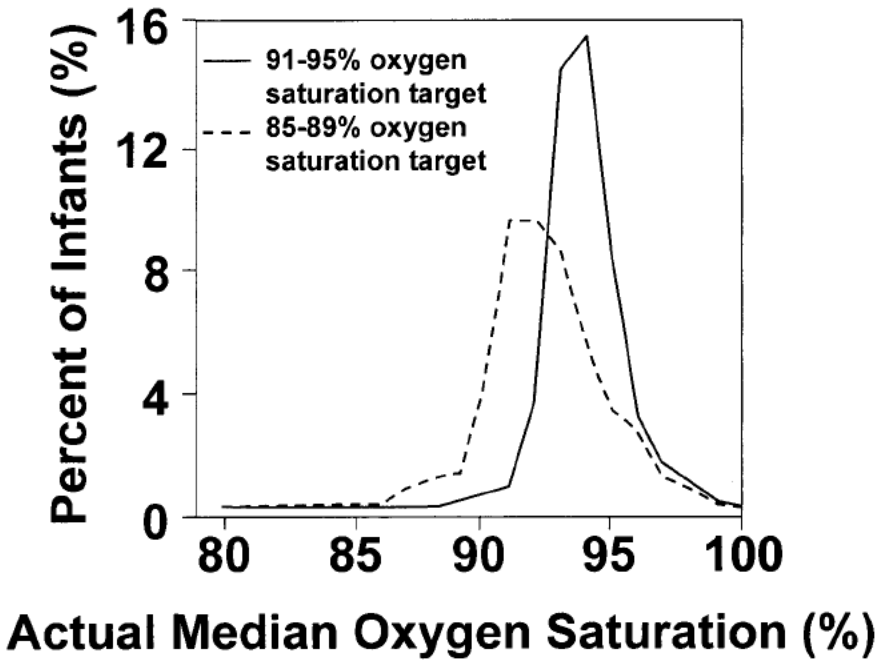
Figure 2



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Das, Abhik
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Gantz, Marie
Subject: RE: Neil"s paper
Date: Monday, November 02, 2009 12:14:11 PM
Attachments: SUPPORT CPAP vs Surf Oct 31 09 adrev.docx

Neil:

Here are some suggested changes and comments. I tried to tone things down a little more without changing the thrust of the conclusions.

I also wonder whether we should proactively state that although death was a pre-specified secondary outcome, we did not pre-specify looking within strata, but felt compelled to present the death results by strata anyway because of safety concerns.

Also, we are reporting a lot of p values without any multiplicity adjustments. Perhaps we can preempt any criticism on that score by stating that as a limitation in the Discussion (adding that readers are free to apply their own significance cut-off, or take these as exploratory, not confirmatory, results)?

Thanks

Abhik

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Saturday, October 31, 2009 4:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz, Marie
Subject: RE: Neil's paper

Hi Everyone
Here is my revised take - please review carefully and see if I have defended our position - I think we make our case. The ROP adds to the benefit and we do not have any increase in any adverse outcomes and I have not overplayed the decrease in death Be well Look forward to your input Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 9:23 AM
To: Finer, Neil; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'mgantz@rti.org'
Subject: Neil's paper

Neil
I have the copy of the paper from Tuesday evening that you sent and have the following comments;

The conclusions of the abstract should state something like intubation with surf offers no benefit over cpap in our study. Should we also state that this occurred in the era of antenatal steroid use as a standard practice and the 96 percent of our infants had received them??

In the methods sample size discssion, do we need to inclde the FU power analysis since we are not yet reporting FU??

Discussion - ors is the first trial to do a head-to-head comparison of cpap versus intubation + surf. We should get this in there.

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The may Ellen Avery survey paper about BPD from 1987 is not in the references - it may be appropriate to include.

I also pulled the May 2009 NeoProm update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. - see the previous email for NICHD and NHLBI discussions.

Thanks for all the effort!!!
This is a landmark study

Rose

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Word count:

Abstract: 250

Manuscript: 3069

Running head: Early CPAP versus Surfactant and outcomes of prematurity

Key words: CPAP, bronchopulmonary dysplasia, extremely low birth weight infant, neonatal mortality, surfactant

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to either CPAP initiated in the delivery room, and were subsequently treated using a protocol driven minimal ventilator strategy, ~~Infants randomized~~ or, to surfactant, and were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001) ~~(p<0.001)~~.

Conclusions: The use of surfactant within 1 hour of birth and conventional mechanical ventilation in ELBW infants between 24 and 27 6/7ths weeks gestation at birth, compared to treatment with CPAP and

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a protocol driven minimal ventilator strategy, did not decrease the incidence of death or survival with BPD at 36 weeks. There was also no demonstrable increase in any adverse neonatal outcomes in infants treated with CPAP. The use of CPAP in such infants is thus an effective evidence based alternative to intubation and surfactant.

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Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent

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review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses~~6~~4, and a reduction in death or the need for oxygen at

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28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. ~~We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.~~

Comment [AD1]: I think this can be deleted here because we say it in the Methods section.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also simultaneously randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven

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minimal ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained antenatally. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.-, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

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NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

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These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

~~Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.~~

Comment [AD2]: This is a repeat, and can be deleted.

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Comment [AD3]: I think we need to be consistent in whether we frame the hypothesis as increased survival free of BPD or reduced death/BPD, and the tables should follow that approach.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks by an absolute difference of 10%.~~,~~ ~~(~~Our sample size calculations were based upon~~using~~ the NRN ~~occurrence~~ rate of death or survival with BPD of 67% ~~using~~ from the year 2000 data, a conservative 2% level of significance (to account for two outcomes for each arm of the 2 by 2 factorial design), and a conservative outcome rate of 50%.~~), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%.~~ Based on a historic intra-cluster correlation of 0.12 in this outcome (from analysis of 2000 NRN data), w~~W~~e further increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment, because ~~as~~ this introduced a clustering effect into the design.~~, and increased the sample sizes by a further~~We inflated the required sample size by an additional 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

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In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

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Statistical analyses: Intent~~ion~~-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided p~~P~~ value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock and ~~(~~O'Brien-Fleming~~)~~ boundaries were used to develop stopping rules for interim safety and efficacy monitoring respectively. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

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Results:

There were 1316 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial ~~was continued~~resumed in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no statistically significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

There was no statistically significant difference in the primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age, between the treatment groups. A trend towards reduced death or BPD was however noted ~~was non-significantly reduced~~ for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, p=0.06~~0~~) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group

Comment [AD4]: I want to say this upfront just to satisfy the NEJM!

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overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,~~,~~ 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.0001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). There was a trend towards reduced incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] ~~was non-significantly reduced~~ in ~~in~~ the CPAP compared to the surfactant infants, ~~(~~23% vs 31%, RR=0.75(0,54, 1.05).

Strata Results: 24 – 25 weeks Gestation

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There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized, 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this stratuma.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, mean of 40.6 vs 47.1 days, p=0.01, and lesser days of mechanical ventilation, mean of 11.3 vs 14.9 days, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

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Our study differs from the recently reported COIN trial[1514] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven minimal ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven minimal ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that the use of surfactant within 1 hour of birth and conventional mechanical ventilation in ELBW infants between 24 and 27 6/7ths weeks gestation at birth, compared to treatment with CPAP and a protocol driven minimal ventilator strategy, does not decrease the incidence of death or survival with BPD at 36 weeks. Our data indeed suggests that early CPAP ~~and protocol driven mimimal ventilator strategy when~~ compared with surfactant ~~given within 1 hour of birth was~~ is associated with a ~~reduction non significant~~ decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a ~~very~~ substantial (and statistically significant) 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with trends

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towards reductions in BPD, ROP, -significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes -represents a substantial clinical benefit compared with the initial use of early surfactant~~,~~.

Comment [AD5]: I am worried that this statement will be perceived to be stronger than our data allow. After all, the reduced deaths are only in the 24-24 weekers.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of air leaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in air leaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of CPAP and a protocol driven minimal ventilator strategy, ~~surfactant within 1 hour of birth~~ ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with ~~CPAP and a protocol driven minimal ventilator strategy~~ surfactant within 1 hour of birth do

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not have a ~~non-significant~~ decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA. There is a strong trend towards reduced death or BPD in the CPAP group with no demonstrable increase in any adverse -neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

COMMENT ON TABLES: All tables need to have adjusted p values. Also, if we are presenting a table for the 24-25 weekers, we need to do the same for the 26-27 weekers. We also need a CONSORT flow chart that should be referenced in the Results section.

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From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; "wcarlo@peds.uab.edu"; "adas@rti.org"; "mgantz@rti.org"
Subject:	RE: Neil"s paper
Date:	Saturday, October 31, 2009 4:35:12 PM
Attachments:	Tables Oct 31 09.docx SUPPORT CPAP vs Surf Oct 31 09 doc.docx

Hi Everyone
Here is my revised take - please review carefully and see if I have defended our position - I think we make our case. The ROP adds to the benefit and we do not have any increase in any adverse outcomes and I have not overplayed the decrease in death
Be well
Look forward to your input
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 9:23 AM
To: Finer, Neil; 'wcarlo@peds.uab.edu'; 'adas@rti.org'; 'mgantz@rti.org'
Subject: Neil's paper

Neil
I have the copy of the paper from Tuesday evening that you sent and have the following comments;

The conclusions of the abstract should state something like intubation with surf offers no benefit over cpap in our study. Should we also state that this occurred in the era of antenatal steroid use as a standard practice and the 96 percent of our infants had received them??

In the methods sample size discssion, do we need to inclde the FU power analysis since we are not yet reporting FU??

Discussion - ors is the first trial to do a head-to-head comparison of cpap versus intubation + surf. We should get this in there.

The may Ellen Avery survey paper about BPD from 1987 is not in the references - it may be appropriate to include.

I also pulled the May 2009 NeoProm update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. - see the previous email for NICHD and NHLBI discussions.

Thanks for all the effort!!!
This is a landmark study

Rose

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	03681
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0978

Table 2. Delivery Room interventions

Variable	CPAP (N=663)	Surfactant (N=653)	P-value
Apgar at 1 minute <3	23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3	4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)	66% (435/662)	93% (606/652)	<0.0001*
Intubated in DR (SUPP03)	34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation	33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)	14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)	67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)	5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)	2% (13/660)	4% (27/653)	0.0225*

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9630
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	100.4 ± 42.9	101.4 ± 41.6	0.7047
Days on supplemental oxygen (survivors only)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors only)	20.0 ± 23.9	23.2 ± 26.2	0.0331
Discharge on oxygen	22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days	55% (362/655)	49% (318/652)	0.0188
Any air leak in first 14 days	7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC	13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery	11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4	14% (92/642)	11% (72/628)	0.1279
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0005

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/280)	0.5217
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.7 ± 47.9	119.2 ± 40.5	0.7394
Days on supplemental oxygen (survivors only)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors only)	33.1 ± 27.3	37.5 ± 29.0	0.1138
Discharge on oxygen	32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days	34% (97/283)	26% (74/280)	0.0429*
Any air leak in first 14 days	8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC	15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery	16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4	20% (54/273)	17% (45/265)	0.4022
Postnatal steroids for BPD	13% (36/276)	20% (54/264)	0.0209*

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a protocol driven minimal ventilator. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen.

Results: The study enrolled 1316 infants. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required intubation or post natal steroids for BPD, (p<.001) (p<0.001).

Conclusions: The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

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Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

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There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[678] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[91011]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1213] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [14]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[15] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses46, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the

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SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network (Clinical Trials Gov. Number, NCT 00233324).This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a protocol driven minimal ventilator strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without

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known malformations, and for whom parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume

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and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

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Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [16,17]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed

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as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more

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epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was non-significantly reduced for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, $p=0.060$) when adjusted for gestational age, center and familial clustering as prespecified. Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata,, 24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, $p=0.03$, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.019$). There were no significant

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differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005). The incidence of retinopathy of prematurity using the new Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[18] was non- significantly reduced in in the CPAP compared to the surfactant infants, (23% vs 31%, RR=0.75(0,54, 1.05)

Strata Results: 24 – 25 weeks Gestation

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical

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ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first prospective randomized multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants and the only prospective randomized trial comparing CPAP to any other outcome that enrolled infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[19] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[20]

Our study differs from the recently reported COIN trial[15,16] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP and a protocol driven minimal ventilator strategy with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a protocol driven minimal ventilator strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation, and the current practice of a number of NRN units.[6,7] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and protocol driven mimimal ventilator strategy when compared with surfactant given within 1 hour of birth was associated with a reduction non-significant decrease in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49%. We also noted a very significant 8% reduction in death in the CPAP infants of our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with reductions in BPD, ROP, significantly decreased durations of ventilation and oxygen, a decreased need for intubation and exposure to post natal steroids in the overall CPAP group without any increase in adverse neonatal outcomes represents a substantial clinical benefit compared with the initial use of early surfactant,.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively

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agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival without neurodevelopmental impairment at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

Compared with the use of surfactant within 1 hour of birth ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol driven minimal ventilator strategy have a non significant decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP is associated with a significant reduction in mortality in the most immature infants. The use of CPAP in such infants is an effective evidence based alternative to intubation and surfactant.

---

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From: Wally Carlo, M.D.
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Urgent;Fw: Manuscript
Date: Saturday, October 31, 2009 2:05:04 PM

Stephanie:

You can correct it all and them I will replace mine with your.

THANKS.

Wally

Wally Carlo, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 11:23 AM
To: Archer, Stephanie (NIH/NICHD) [E]; 'nfiner@ucsd.edu'; Wally Carlo, M.D.
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: Urgent;Fw: Manuscript

Stephanie
I looked at the boilerplate in detail for Wally's paper.
I will repoll the steering committee regarding CTSA support and this will need to be accurately updated.
Emory has indicated an alternate author.
For individual site grant numbers, please list the U10 awards first (they funded the vast majority of study costs, the GCRCs and CTSA funding was much less).

Please affirm/check the following items:
Mickey's institution name - I believe this is North Shore, but check with him or his staff. Also his tenure for the NRN should be 2006-present in stead of 2011.

Did indiana indicate that
Faithe Hamer had a role (in addition to FU)?

RTI listing should also include Dennis Wallace, PhD.

Does UCSD need to include Rene Bridges? She responded to several of the queries I sent over time.

Does Iowa need to list Gretchen - one of the other research nurses?

University of New Mexico - Conra Lacy is not listed, yet she is the lead coordinator. -please check.

UT southwestern - Diana Vasil is not listed and has also been involved with query resolution.

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The DSMC is missing and needs to be listed.

We should also list the NHLBI folks. I will get a lis of them.

Let me know if you need help getting responses. This is a pivotal trial and I want to get it right.

Thanks so much for putting this together.

Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>
Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

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525 New Hillman Building
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From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oct 31-Nov 3
Date: Saturday, October 31, 2009 2:02:18 PM

Rose:

One of the most important things we can do is (b) (6)
You need to do it. Will try not to bother you.

Wally

Wally Carlo, M.D.
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 31, 2009 11:23 AM
To: 'nfiner@ucsd.edu'; Wally Carlo, M.D.
Subject: Oct 31-Nov 3

Neil and Wally -
Thanks to the two of you for the immense commitment to the SUPPORT trial.
I truly appreciate the professional as well as personal investment that you have made to help babies!!

Just in case -
(b) (6)

I can be reached via Blackberry and cell phone (703-395-(b) (6)

Unfortunately, we have an issue with the land line phone (b) (6)
(b) (6) so I may not have immediate access to computer applications. If needed, I can get to an internet wireless or line hook up with short notice.

I will be back in the office on Wednesday, november 4. I will be available for the dsmc on Wednesday.

With warmest regards,

Rose

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mgantz@rti.org; adas@rti.org
Cc: mcunningham@rti.org; Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; petrie@rti.org
Subject: RE: Manuscript
Date: Saturday, October 31, 2009 2:01:14 PM

Hi Rose:

Thanks for going so carefully through it. I will work on it right away.

Wally

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Sent: Saturday, October 31, 2009 11:23 AM
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Cc: 'mcunningham@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'petrie@rti.org'
Subject: Re: Manuscript

Wally

Thanks for quickly turning this around.

We refer ro nonrandomized studies in several sections of the paper. Is observational a better word?

There is no citation of the STOP-ROP paper in the manuscript. Although this looked at saturation levels in pretheshold ROP, it should probably be listed.

Methods - end of the first paragraph - delete "before delivery" as part of the consent process. Although this occrred in the vast majority, there were a few that occurred after delivery for a variety of reasons.

Wold it be possible to include the scatter graph of actual versus monitor oximetry levels included in the stdy protocl in the supplementary/appendix materials? We explain this 3 percent offset in the methods on page 12, bt the graph really shows it to those who are visually oriented.

At the bottom of page 12 we stated that sat targets were maintained by "clinicians.". It may be more accurate to say adjustments.... were performed by "NICU or clinical staff.". This way, everyone (nrse, md, resp therapist) are included and it is acucrate reporting.

In the methods section (page 13) nder assessments - should we (or do we even have space) report abot the 14 day safety monitoring??

Leave 18-22 month FU out of the methods section on page 13 I this shold be incluuded in the discussion.

Bottom of page 14 I should we add one sentence about the first dsmc look at the data that occurred due

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to concern with compliance with sat levels are the part of the investigators as this happened prior to 25 percent enrollment? I suggest "dsmc evaluated sat data upon reqest of investigators to evaluate compliance after enrollment of XX infants.". You do explain this in the results and it leaves the reader wondering why we did this.

Results - first line page 15 I enrollment started in Feb 2005 not Jan 2004 (I think).

Discussion - second line - you stated "standard" practice. I recommend changing this to "common" practice as there was no AAP guideline or otherwise indicating "standard."

Page 17 - end paragraph- reviewers may want to know abot the lower sat infants and deaths (ron goldberg's comment at the sc meeting.

The last paragraph of the discussion should restate the primary outcome and the two significant otcones of ROP and BPD benefit.

Table 1 has 655 in low sat group and 661 in high sat group. On table 2 many of the denominators are 654 in low sat group and there is a denominator of 662 on several of the high sat outcomes - we need to fix this.

Also, threshold rop/death says 17/605 for low sat group (should be 170/) and high sat group says 198.616.

Figure 1 - is there a way to have "pregnancies" assessed for eligibility?". That is actually how this nfolded.

For figure 2 - is there any way to "statistically" assess if we reached an adequate separation between the two groups??

Also -
I also pulled the May 2009 NeoProm confidential update.
As of that meeting, the following nmbers were recruited into the trials:

BOOST II australia 658/1200
BOOST II New zealand -291/320
BOOST UK -332/1200
COT -684/1200

Each trial has a dsmc and likely monitoring AE's like mortality. I have spoken to NICHD and NHLBI leadership. The other trials are enrolling children following delivery. Our dsmc meets Nov 4 -the leadership would like input from or DSMC prior to any possible confidential dscussions with other dsmc's. Also the observed mortality between the two sat groups (16 and 20 percent) is tighter than the nrn range of mortality from historical data provided to our dsmc (9.5-32 percent deaths by day 14).

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Das, Abhik <adas@rti.org>
Cc: Cunningham, Meg <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Fri Oct 30 18:02:10 2009
Subject: FW: Manuscript

Dear Rose, Neil, Marie and Abhik:

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I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

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From: Kathryn Fallon
Sent: Friday, October 30, 2009 4:54 PM
To: Wally Carlo, M.D.
Subject: Manuscript

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From:	Finer, Neil
To:	Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Cc:	Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Rich, Wade
Subject:	RE: Manuscript
Date:	Friday, October 30, 2009 8:56:11 PM
Attachments:	Oxygen Saturation Target 10 30 09 NF Rev.doc

Hi Wally

Very nice, succinct. I removed one sentence that I think is redundant in the intro. Marie can you please add all the relevant p values and then we can send out to the Subcommittee

Thanks for a wonderful effort Wally

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, October 30, 2009 3:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; Das, Abhik
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
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10/30/09
6.0

Randomized Trial of Higher Versus Lower Oxygen Saturation Targeting in Extremely Premature Infants

Waldemar A. Carlo, MD[1]; Neil N. Finer, MD[2]; Michele C. Walsh, MD MS[3]; Wade Rich, RRT[1]; Marie Gantz, PhD[4], Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[5], Abhik Das, PhD[7]; W. Kenneth Poole, PhD[4]; Kurt Schibler, MD[8]; Nancy Newman, RN[3]; Ivan D. Frantz III, MD[9], Pablo J. Sánchez, MD[10], Susie Buchter, MD[11]; Brenda H. Morris, MD[12]; Nirupama Laroia, MD[13]; Brenda B. Poindexter, MD MS[14]; C. Michael Cotten, MD MHS[15]; Krisa P, Van Meurs, MD[16]; Beena Sood. MD, MS[17]; Shahnaz Duara, MD[18]; T. Michael O'Shea, MD, MPH[19]; Edward F. Bell, MD[20]; Richard A. Ehrenkranz, MD[21]; Kristi L. Watterberg, MD[22]; Rosemary D. Higgins, MD[23]; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [2]University of California at San Diego, San Diego, CA; [3]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [4]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [5]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6]Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; [7]Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8]Department of Pediatrics, University of Cincinnati, Cincinnati, OH; [9]Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center,

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Boston, MA; [10]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [11]Emory University School of Medicine; Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [12]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [13]University of Rochester School of Medicine and Dentistry, Rochester, NY; [14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [15]Department of Pediatrics, Duke University, Durham, NC; [16]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA; [17]Department of Pediatrics, Wayne State University, Detroit, MI; [18]University of Miami Miller School of Medicine, Miami, FL; [19]Wake Forest University School of Medicine, Winston-Salem, NC; [20]Department of Pediatrics, University of Iowa, Iowa City, IA; [21]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [22]Univresity of New Mexico Health Sciences Center, Albuquerque, NM; [23]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Corresponding author and reprints:

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Acknowledgements

The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2005-2009).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Case Western Reserve University Rainbow Babies & Children's Hospital (GCRC M01 RR80, U10 HD21364) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN.

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Cincinnati Children's Hospital Medical Center University of Cincinnati Hospital and Good Samaritan Hospital (GCRC M01 RR8084, U10 HD27853) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Kathy J. Auten, MSHS; Kimberly A. Fischer, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (CTSA UL1 RR25008, GCRC M01 RR39, U10 HD27851) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (CTSA UL1 RR25761, GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Diana D. Appel, RN BSN; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

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RTI International (U01 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (CTSA UL1 RR25744, GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death. As part of the SUPPORT Trial, infants were also randomized to continuous positive airway pressure and a protocol-driven limited ventilator strategy or to surfactant and ventilation.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; P = ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; P = 0.__) and was partially offset a lower rate of threshold retinopathy (9 vs 18%; RR 0.51, 0.37, 0.71; P = ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease combined outcomes of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in

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threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly being advocated as it has short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. ~~Pulse oximetry has become the standard technique for continuous monitoring of oxygenation.~~ While data from these recent prospective observational and retrospective studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

Comment [A1]: Previously stated above

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent Data Coordinating Center for the NRN (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

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Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation, without a decision to forego resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) with balancing blocks. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[20] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinicians, not by the research staff. Reports of displayed data by treatment arm and clinical center were

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provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2 factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy..

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge except for retinopathy. Outcomes included only predefined clinical diagnoses and potential adverse events. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Follow-up at 18-22 months is being conducted.

Statistical analysis

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The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturations between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1310 infants for 80% power to detect a 10% difference in outcome assuming a baseline estimated rate of 50% of death/threshold retinopathy/surgery. This sample size estimate included an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. While these sample size calculations allowed for the testing of two co-primary outcomes for the two interventions (oxygen saturation targeting and protocol-driven, limited ventilator strategy) of this 2 by 2 factorial trial, the trial was not powered to determine an interaction between the interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock

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(O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; P=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; P=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was decreased in the lower oxygen saturation targeted group (9 vs 18%; CI 0.51, RR 0.37, 0.71; P=0._____).

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Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test on oxygen at 36 weeks and bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies, and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered for a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction among the outcomes evaluated. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation in previous randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[23] At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim

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analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	17/605 (28)	198.616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.6)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.9, 1.1)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.8, 1.4)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.8, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (7)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

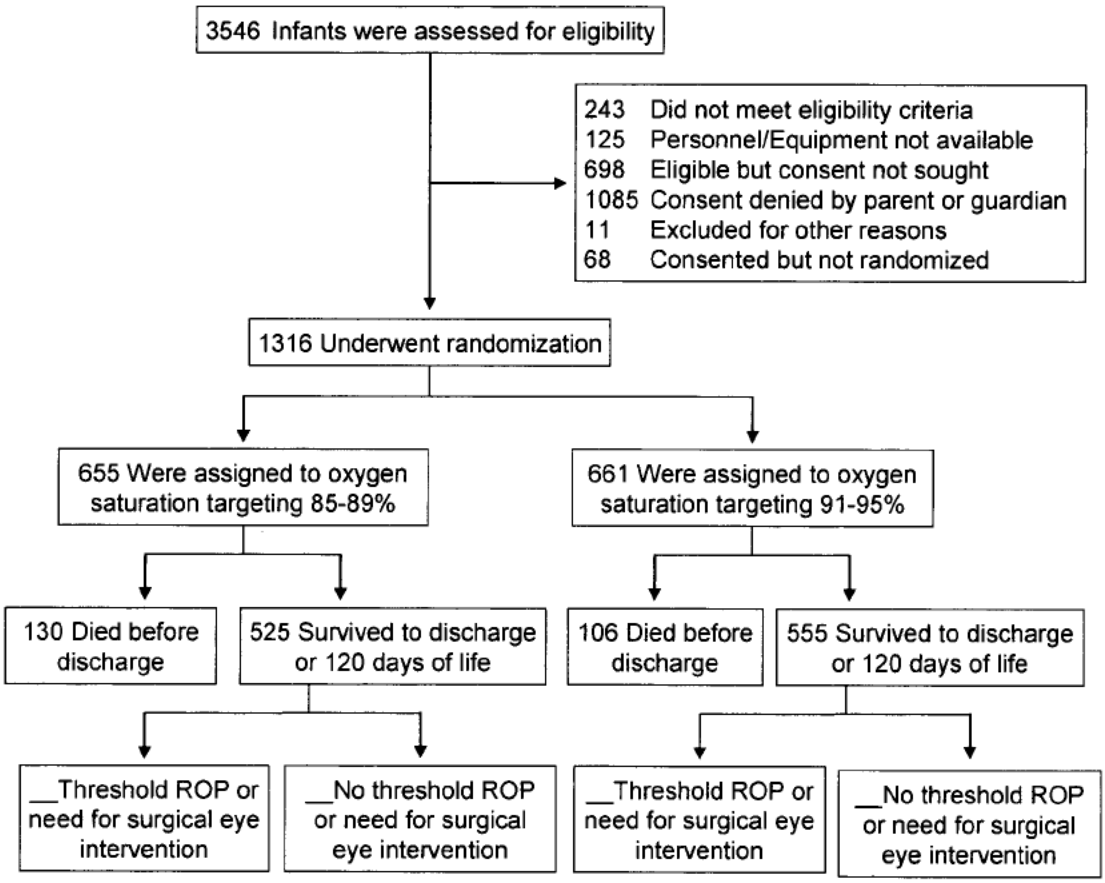

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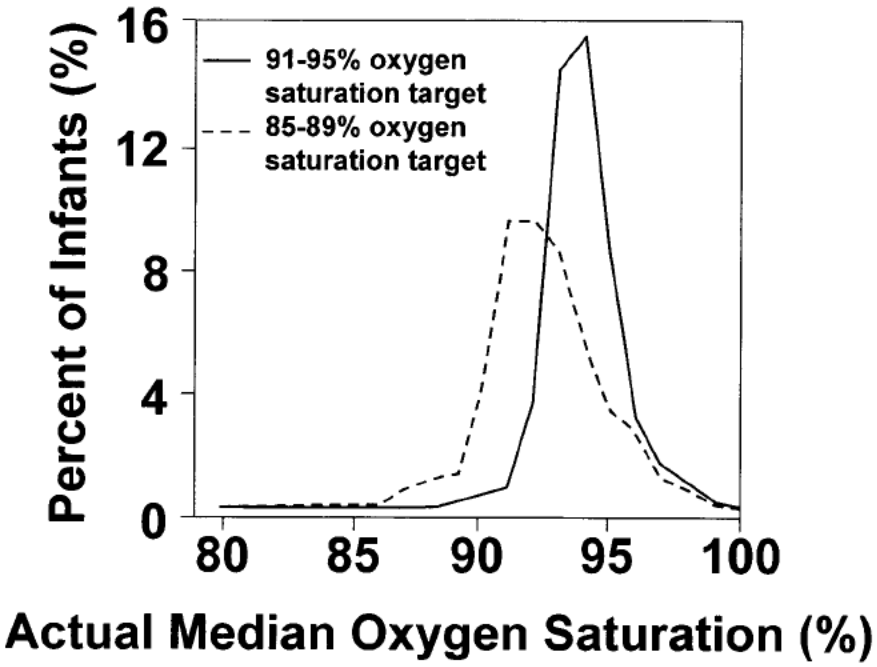
Figure 2



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The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Gantz, Marie; Das, Abhik
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: FW: Manuscript
Date: Friday, October 30, 2009 6:02:15 PM
Attachments: Oxygen Saturation Target 10 30 09.doc

Dear Rose, Neil, Marie and Abhik:

Enclosed is the next draft. I have received comments from some of you and from Michele, and I have responded to the issues raised.

I talked with Abhik and he agreed Marie should get a Kaplan Meier plot for mortality (New Fig 2).

I think it is ready to be sent to the rest of the Subcommittee.

Wally

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Subject: Manuscript

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Randomized Trial of Higher Versus Lower Oxygen Saturation Targeting in Extremely Premature Infants

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity and/or death. As part of the SUPPORT Trial, infants were also randomized to continuous positive airway pressure and a protocol-driven limited ventilator strategy or to surfactant and ventilation.

Results

Threshold retinopathy/death did not differ between the lower and higher oxygen saturation target groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; P = ___). Death was more frequent in the lower oxygen saturation target group (20 vs 16%; RR 1.27; CI 1.01, 1.60; P = 0.__) and was partially offset a lower rate of threshold retinopathy (9 vs 18%; RR 0.51, 0.37, 0.71; P = ___).

Conclusions

Lower oxygen saturation (85-89%) targeting did not significantly decrease combined outcomes of threshold retinopathy/death but resulted in an increase in mortality that partially offset a decrease in

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threshold retinopathy. The increased mortality is of concern as lower saturation targeting is increasingly being advocated as it has short term retinopathy benefits (Clinical Trials Gov. Number, NCT 00233324).

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation. Associations of lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years.[3,4,5,15,16] In a survey study of 144 neonatal intensive care units, the rate of retinal ablation surgery was higher in infants cared for in neonatal intensive care units with maximum target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] The incidence of severe retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90% in a retrospective study comparing outcomes at five neonatal intensive care units.[3] Rates of mortality and cerebral palsy did not differ between these units. In three other studies, a policy of oxygen saturation targeting of approximately 83

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to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Furthermore, mortality and neurodevelopmental outcomes were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from these recent prospective observational and retrospective studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and protocol-driven limited ventilator strategy. The oxygen saturation part of the trial tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity or death among infants of 24 to 27 weeks gestational age at birth. The ventilation part of this factorial design trial was used to control for the ventilatory approach and test other hypotheses.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International, the independent Data Coordinating Center for the NRN (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

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Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestation, without a decision to forego resuscitation were eligible for enrollment at birth. Outborn infants and major congenital anomalies were excluded. Multiple births were randomized to the same treatment arm.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed opaque envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% (the lower and higher oxygen saturation target groups, respectively) with balancing blocks. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[20] Thus, for example, an oxygen saturation display of 92% would correspond to an actual oxygen saturation of 89% and 95% in the 85-89% and 91-95% target groups, respectively. The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommended in the protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximeter. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinicians, not by the research staff. Reports of displayed data by treatment arm and clinical center were

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provided quarterly for feedback on targeting performance. For the ventilation part of this 2 by 2 factorial design trial, participants were also randomly assigned to continuous positive airway pressure with a protocol-driven limited ventilatory strategy or to prophylactic/early surfactant with a protocol-driven conventional ventilation strategy..

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge except for retinopathy. Outcomes included only predefined clinical diagnoses and potential adverse events. The primary outcome was death before discharge and/or threshold retinopathy. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical ophthalmologic interventions defined as any of the following: laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin).

Follow-up at 18-22 months is being conducted.

Statistical analysis

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The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment arm who developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for familial clustering due to randomization of multiple births to the same treatment arm. A median actual oxygen saturation value while on oxygen supplementation was determined for each infant to compare the effect of targeting an actual oxygen saturations between treatment arms.

An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1310 infants for 80% power to detect a 10% difference in outcome assuming a baseline estimated rate of 50% of death/threshold retinopathy/surgery. This sample size estimate included an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. While these sample size calculations allowed for the testing of two co-primary outcomes for the two interventions (oxygen saturation targeting and protocol-driven, limited ventilator strategy) of this 2 by 2 factorial trial, the trial was not powered to determine an interaction between the interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent Data Safety and Monitoring Committee appointed by the Director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock

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(O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage, and a combination of any of the above events.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee and decision of the National Institutes of Child Health and Human Development Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and continued enrollment was approved.

The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The primary outcome, threshold retinopathy and/or death before discharge, did not differ between the lower and higher oxygen saturation groups (28 vs 32%; CI 0.90; RR 0.76, 1.06; P=0.____; Table 2). Death before discharge occurred in 130 of the 654 (20%) of the infants in the lower oxygen saturation group versus in 107 of the 662 (16%) of the infants in the higher oxygen saturation group (RR 1.27; CI 1.01, 1.60; P=0.04). Comparable results were observed for both gestational age strata. Kaplan Meier Analysis indicated _____ (Figure 2). Mortality in the first and second weeks after birth was not significantly different between the two treatment groups (Table 2). Threshold retinopathy was decreased in the lower oxygen saturation targeted group (9 vs 18%; CI 0.51, RR 0.37, 0.71; P=0._____).

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Oxygen use at 36 weeks was decreased in the lower oxygen saturation group but bronchopulmonary dysplasia determined by the physiological oxygen saturation test on oxygen at 36 weeks and bronchopulmonary dysplasia/death did not differ between the treatment groups. Other pre-specified major outcomes did not differ significantly between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was overlap (Figure 3). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies, and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and the limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians in an attempt to decrease retinopathy of prematurity. However, even though lower oxygen saturation targeting reduced threshold retinopathy, it also increased the risk for mortality.

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This trial was not powered for a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction among the outcomes evaluated. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group[1], which is close to the 3.8% mortality increase in the lower targeted SpO2 group that was observed in our trial.

Restriction of oxygenation in previous randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group which are closer to the targets of the higher saturation arm in the current trial. The lower target of oxygen saturations or the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[23] At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so that appropriate decisions can be made regarding their interim

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analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group n/N (%)	Higher Saturation Group n/N (%)	Adjusted Relative Risk[1] (95% CI)
Threshold retinopathy/death	17/605 (28)	198.616 (32)	0.90 (0.76, 1.06)
Threshold retinopathy	43/483 (9)	95/514 (18)	0.51 (0.37, 0.71)
Death before discharge	130/654 (20)	107/662 (16)	1.27 (1.01, 1.6)
Death by 7 days	41/654 (6)	38/661 (6)	1.11 (0.72, 1.72)
Death by 14 days	64/654 (10)	56/661 (8)	1.2 (1.2 (0.84, 1.7)
Death by 36 weeks	114/654 (17)	94/662 (14)	1.27 (0.99, 1.63)
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	202/540 (37)	265/568 (47)	0.81 (0.71, 0.92)
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	316/654 (48)	359/662 (54)	0.91 (0.82, 1.01)
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	205/540 (38)	237/568 (42)	0.92 (0.81, 1.05)
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	319/654 (49)	331/662 (50)	0.99 (0.9, 1.1)
Intraventricular hemorrhage, grade 3 or 4	83/630 (13)	81/640 (13)	1.06 (0.8, 1.4)
Intraventricular hemorrhage, grade 3 or 4 or death	179/653 (27)	156/661 (24)	1.18 (0.99, 1.42)
Periventricular leukomalacia	24/631 (4)	30/641 (5)	0.83 (0.49, 1.42)
Periventricular leukomalacia or death	149/654 (23)	132/662 (20)	1.18 (0.96, 1.45)
Necrotizing enterocolitis, stage ≥ 2	76/641 (12)	70/649 (11)	1.11 (0.82, 1.51)
Necrotizing enterocolitis, stage ≥ 2 or death	176/654 (27)	155/662 (23)	1.18 (0.98, 1.43)
Late onset sepsis	228/624 (37)	226/634 (36)	1.03 (0.89, 1.18)
Late onset sepsis or death	300/654 (46)	291/662 (44)	1.05 (0.94, 1.18)
Patent ductus arteriosus	307/641 (48)	324/648 (50)	0.96 (0.86, 1.07)
Medical treatment for patent ductus arteriosus	219/634 (36)	233/645 (36)	0.95 (0.82, 1.09)
Surgical treatment for patent ductus arteriosus	73/641 (11)	68/648 (11)	1.09 (0.8, 1.48)
Pneumothorax – no. (%)	47/654 (7)	42/662 (7)	1.12 (0.74, 1.68)

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Any air leaks – no. (%)	51/654 (8)	42/662 (6)	1.23 (0.83, 1.83)
Postnatal steroids for bronchopulmonary dysplasia	61/636 (10)	69/644 (11)	0.91 (0.67, 1.24)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.08
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.21
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	<0.001
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.95
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.06
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.50
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

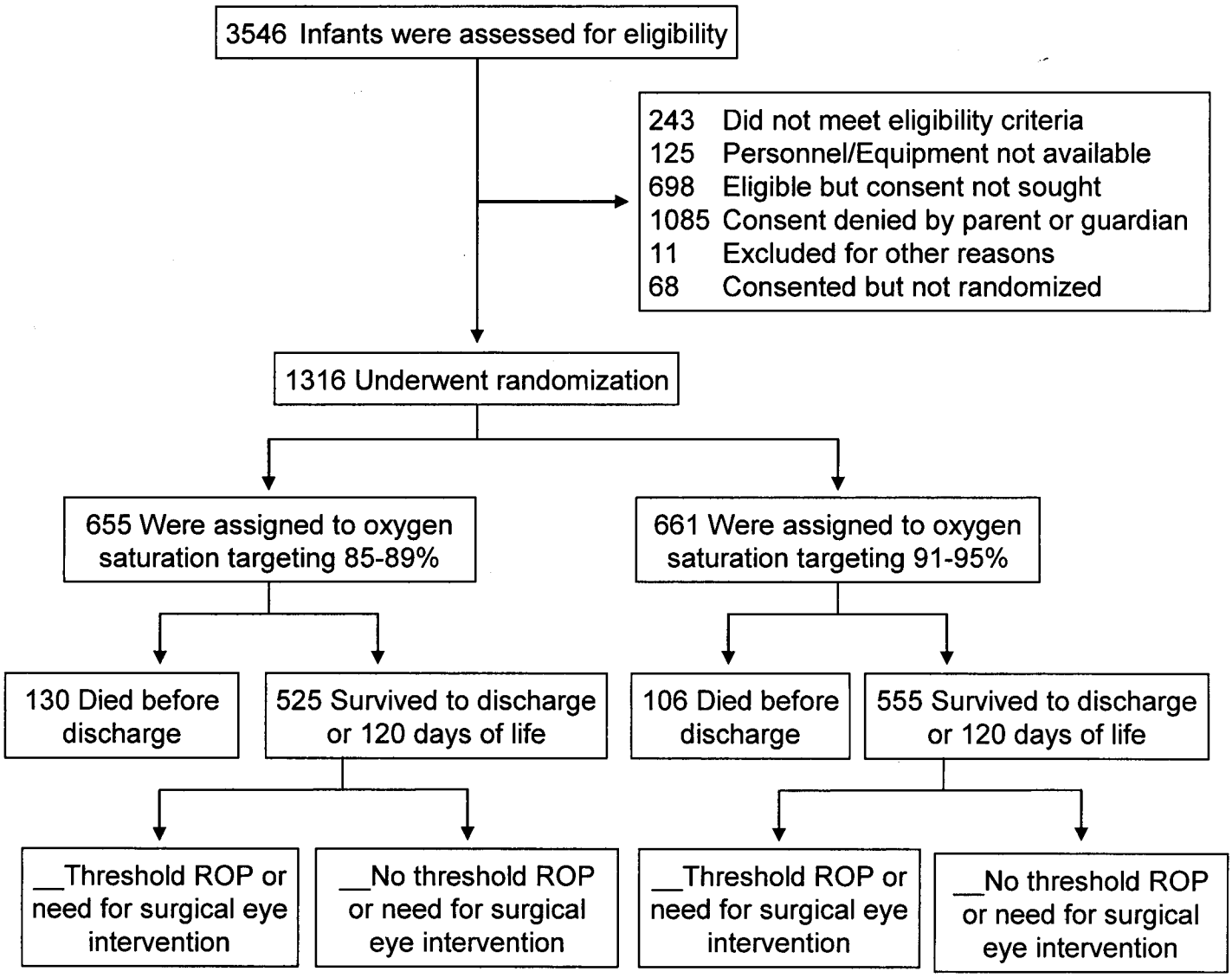

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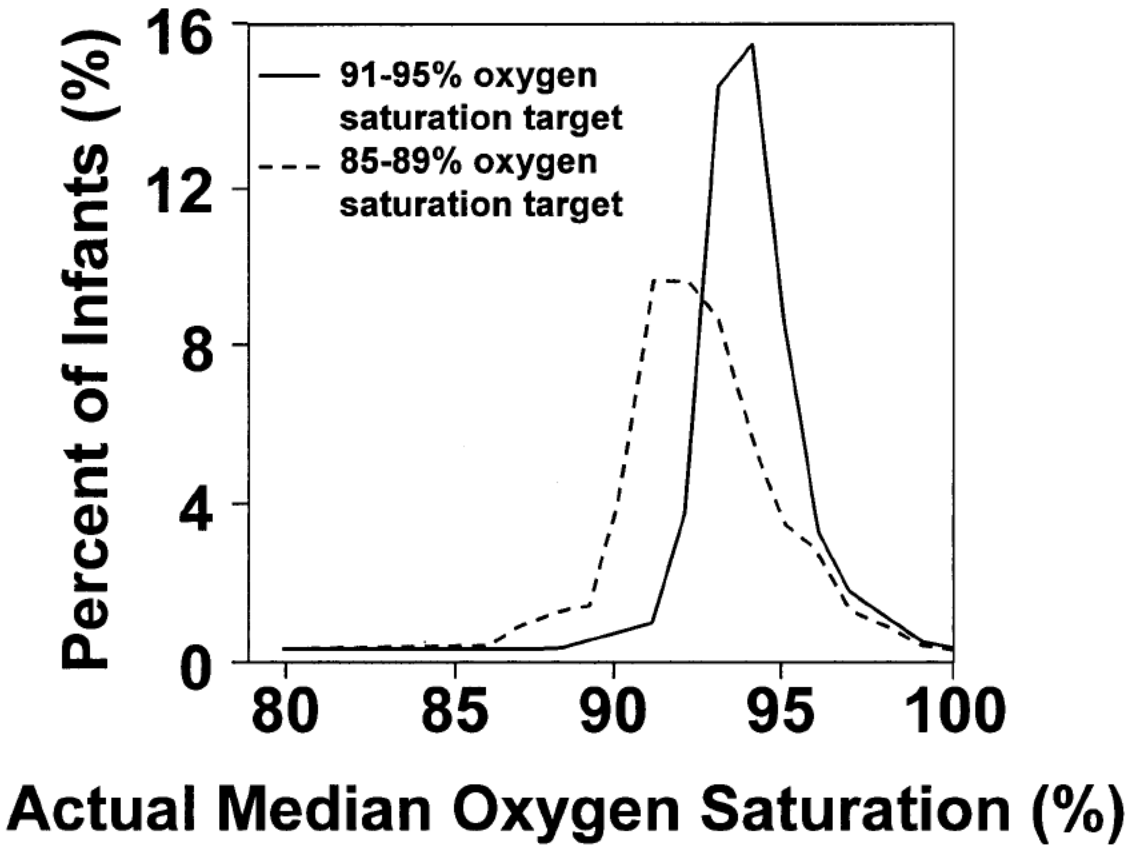
Figure 2



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Author's Contribution Statement/Conflict of Interest Statement:

The authors have seen and approved the final manuscript and have contributed substantially to toe conception and design of the trial, the analysis and interpretation of the data, and the drafting of the manuscript. The undersigned authors warrant that the article is original; does not infringe upon any copyright or other proprietary right of any third party; is not under consideration by another publication and its essential substance, tables, and figures have not been previously published. No author has financial interest in the product tested.

Each of the authors signing below attests by his/her signature that he/she has read the final manuscript, approved it, and assures the integrity of the work. Each also attests that he/she has fulfilled the criteria of the Uniform Requirements for manuscripts Submitted to Biomedical Journals. Dr. Waldemar A. Carlo is the corresponding author for the manuscript: his contact information appears on the title page of the paper.

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From: Wally Carlo, M.D.
To: Alexis Davis; Krisa Van Meurs; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ANS manuscript follow-up
Date: Friday, October 30, 2009 5:54:58 PM

Alexi:

I am very busy trying to get the O2 sat draft out today and working on it during the weekend so will attend to this. Please do not contact Scott now as we have agreed to have one final request from the committee to him.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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Phone: 205 934 4680
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From: (b) (6) [mailto (b) (6) **On Behalf Of** Alexis Davis
Sent: Friday, October 30, 2009 4:33 PM
To: Wally Carlo, M.D.; Krisa Van Meurs; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: ANS manuscript follow-up

Hi Dr. Carlo-

Just wanted to summarize what still needs to be done and we go from here regarding the antenatal steroids manuscript:

1) Redo the existing analysis to extend to 2006 or 2007 (2007 would be a 15 year cohort). This would impact all existing figures and tables, including:
- Figure 1: rates of ANS administration by GA (22-25 weeks) over the study period
- Table 1: demographics of study population
- Table 2: rates of death and morbidities and RR to compare ANS/no ANS in each GA group (22-25 weeks)
- Figure 2: Cox regression of time to death comparing ANS/no ANS (I don't have this figure; is this ANS vs. no ANS in only 22-23 weekers or all GAs?)
- Table 3: 18-22 month outcomes
- redo interaction analyses (no figure/table in manuscript)

**Alexis can contact Scott to start working on this

2) additional analyses to consider
- adding a second Y axis (or separate symbols) to Figure 1 to reflect the proportion of 22-23 weekers as a percentage of the study population over time
- adding a "death or major morbidity" (DOMM) composite outcome to Table 2; consider adding ROP to the major morbidities (prior suggestion from Rose on my initial GDB proposal)

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- since an updated analysis would cover such a long study period, consider assessing 23 weekers (and also 22 weekers if their composite data after re-analysis suggests a benefit) for the outcomes of DOMM and Death/NDI and comparing by time epochs to assess to improvements in care over time (I'm thinking 3 epochs: either 3 5-year epochs or pre ACOG/immediately post ACOG/most recent (though I'm not sure there will be sufficient numbers for the earliest epoch); depending on the opinions of the committee, this could also be reversed into survival without morbidity and survival without NDI
- since we are going to have a larger cohort, additional neonatal variables could be added to the 18-22 month outcomes model (i.e. NEC, sepsis, severe IVH/PVL, postnatal steroids, BPD, maybe center) Maybe this was already done, but I didn't see it in my version of the manuscript

**Perhaps Wally can discuss any/all of these with the subcommittee members to determine which to proceed with

3) refresh introduction based on updated 2008 ACOG statement, revise results section based on new analyses, add to discussion section (new articles from 2007/08)

**Alexis can start working on this now

Depending on what additional analyses are done, would it be appropriate to separate this into early and late outcomes manuscripts? It might be interesting to explore the interaction data more if this is the case.

Have a good weekend-
Alexis

--
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data
Date: Friday, October 30, 2009 5:01:00 PM

She is ok with waiting for our DSMC Wednesday and will send us an email copying Dr. Shurin. I also spoke to Dorothy Gail who affirmed their email

Rose

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Friday, October 30, 2009 4:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: NRN Support trial data

If you need me i am available
(b) (6) [redacted]
Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
6100 Executive Blvd
Bethesda MD 20892 (express mail Rockville MD 20852)
Phone 301 435 6894
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Email. Spongc@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Sent: Fri Oct 30 16:22:44 2009
Subject: RE: NRN Support trial data

I will call you in a few minutes

Rose

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, October 30, 2009 4:22 PM
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Yes. Is either of you around now, It is almost 4:30, but I can talk now, sorry but things have been so busyl.

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, October 29, 2009 2:21 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: NRN Support trial data

Dear Dr. Maddox,

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

The NRN's SUPPORT trial data analysis for the primary outcome is complete and we want to bring it to your attention. This trial was a factorial design comparing low oxygen vs. high oxygen by two hours of age; the other comparison was CPAP vs. intubation with surfactant in the delivery room. Attached are some slides with data on the primary analyses. (I am sending this email on behalf of Rose who is at the NRN meeting today).

The primary outcome of death or bronchopulmonary dysplasia for the ventilation arm is no difference between CPAP versus intubation with surfactant, but a strong trend and significant secondary outcomes for the CPAP arm, especially in babies born at 24-25 weeks.

For the low vs. high oxygen comparison, there is no difference in the primary outcome of death or ROP. However there is a significant increase in death (predefined secondary outcome) in the lower saturation group (20%) versus the higher saturation group (16%). Offsetting this, is a significantly lower rate of ROP (9%) in the lower saturation group compared to the higher saturation group (18%). This suggests that there is a (b) (5) [redacted]

There are ongoing saturation trials around the world and we are weighing whether we should share the results confidentially (if that is possible) of the significant increase in death with the DSMCs of the ongoing trials. The ongoing trials have a primary outcome of death or neurodevelopmental impairment at 18-22 months. All of these trials recruit infants after birth; the SUPPORT trial consented mothers prior to delivery. Further, gestational age entry criteria may be slightly different.

The infants are being followed for 18-22 month outcome and the DSMC will meet on November 4th – at that meeting they will review the available follow-up data.

Would you be available for a call to discuss this sometime today or tomorrow?
Warmest regards,
Rose and cathy

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Subject: FW: NRN Support trial data
Date: Friday, October 30, 2009 4:52:00 PM

Here is the NHLBI email
Rose

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, October 30, 2009 10:09 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Dear Rose,
Dorothy and I don't think there is any (b) (5) (b) (5) . You will have the SUPPORT DSMC review the data that is available and they will be able to advise about any pressing concerns.

Carol

Carol J. Blaisdell, M.D.
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Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, October 30, 2009 8:40 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Carol and Dorothy,
I am attaching and explaining what we have thus far. I have attached T2S major outcomes for the high and low saturation groups. The low sat group had a (b) (5) Clearly follow up is warranted.

We do not yet have analyses on (b) (5) .

I have also attached T3 BPD which shows (b) (5) If you go to the second table on the T3 BPD document, you will see that a (b) (5)

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(b) (5) .

If you look at T2 Other outcomes table, you will see that the (b) (5)

I think we have some of the other requested info (b) (5) and I will find them and send them.

I am over at the Bolger center until about 3 today at the NRN Follow Up PI meeting.

Let me know if you have other questions. There has not been a cause of death analysis at this point.

Regards
Rose

Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Thursday, October 29, 2009 6:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Rose/Cathy ==appreciate your concern, but more analysis may help understand if this is real?
Questions:
What were the (b) (5)
If increased (b) (5)
In the intent to treat with (b) (5)
Given that babies (b) (5)

I seem to recall that area under the curve of (b) (5)

How about (b) (5)

Carol
Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, October 29, 2009 5:04 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: Confidential NRN Support trial data

Carol and Dorothy-
Thank you for your support for the SUPPORT study. The subcommittee and steering committee met yesterday and today and has some concerns regarding (b) (5) (b) (5) I am forwarding the primary outcome information and our specific questions for NICHD leadership. I know Carol will be at the dsmc meeting next week.

Your thoughts would be very helpful as there are 3 saturation trials occurring around the world currently. Again- I want to express my thanks for all you involvement and spport.

Rose

From: Spong, Catherine (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Oct 29 14:20:53 2009
Subject: NRN Support trial data

Dear Dr. Maddox,

The NRN's SUPPORT trial data analysis for the primary outcome is complete and we want to bring it to your attention. This trial was a factorial design comparing low oxygen vs. high oxygen by two hours of age; the other comparison was CPAP vs. intubation with surfactant in the delivery room. Attached are some slides with data on the primary analyses. (I am sending this email on behalf of Rose who is at the NRN meeting today).

The primary outcome of death or bronchopulmonary dysplasia for the ventilation arm is no difference between CPAP versus intubation with surfactant, but a strong trend and significant secondary outcomes for the CPAP arm, especially in babies born at 24-25 weeks.

For the low vs. high oxygen comparison, there is no difference in the primary outcome of death or ROP. However there is a significant increase in death (predefined secondary outcome) in the lower saturation group (20%) versus the higher saturation group (16%). Offsetting this, is a significantly lower rate of ROP (9%) in the lower saturation group compared to the higher saturation group (18%). This suggests that there is a (b) (5)

There are ongoing saturation trials around the world and we are weighing whether we should share the results confidentially (if that is possible) of the significant increase in death with the DSMCs of the ongoing trials. The ongoing trials have a primary outcome of death or neurodevelopmental impairment at 18-22 months. All of these trials recruit infants after birth; the SUPPORT trial consented mothers prior to delivery. Further, gestational age entry criteria may be slightly different.

th

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The infants are being followed for 18-22 month outcome and the DSMC will meet on November 4 – at that meeting they will review the available follow-up data.

Would you be available for a call to discuss this sometime today or tomorrow?
Warmest regards,
Rose and cathy

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
6100 Executive Blvd, Rm 4B03, MSC 7510
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data
Date: Friday, October 30, 2009 4:51:00 PM

I am on the phone with her now – will let you know
Rose

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Friday, October 30, 2009 4:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: NRN Support trial data

If you need me i am available
(b) (6)
Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
6100 Executive Blvd
Bethesda MD 20892 (express mail Rockville MD 20852)
Phone 301 435 6894
Fax 301 496 3790
Email. Spongc@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Sent: Fri Oct 30 16:22:44 2009
Subject: RE: NRN Support trial data

I will call you in a few minutes

Rose

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, October 30, 2009 4:22 PM
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Yes. Is either of you around now, It is almost 4:30, but I can talk now, sorry but things have been so busyl.

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, October 29, 2009 2:21 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: NRN Support trial data

Dear Dr. Maddox,

The NRN's SUPPORT trial data analysis for the primary outcome is complete and we want to bring it to

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your attention. This trial was a factorial design comparing low oxygen vs. high oxygen by two hours of age; the other comparison was CPAP vs. intubation with surfactant in the delivery room. Attached are some slides with data on the primary analyses. (I am sending this email on behalf of Rose who is at the NRN meeting today).

The primary outcome of death or bronchopulmonary dysplasia for the ventilation arm is no difference between CPAP versus intubation with surfactant, but a strong trend and significant secondary outcomes for the CPAP arm, especially in babies born at 24-25 weeks.

For the low vs. high oxygen comparison, there is no difference in the primary outcome of death or ROP. However there is a significant increase in death (predefined secondary outcome) in the lower saturation group (20%) versus the higher saturation group (16%). Offsetting this, is a significantly lower rate of ROP (9%) in the lower saturation group compared to the higher saturation group (18%). This suggests that there is a (b) (5) [redacted]

There are ongoing saturation trials around the world and we are weighing whether we should share the results confidentially (if that is possible) of the significant increase in death with the DSMCs of the ongoing trials. The ongoing trials have a primary outcome of death or neurodevelopmental impairment at 18-22 months. All of these trials recruit infants after birth; the SUPPORT trial consented mothers prior to delivery. Further, gestational age entry criteria may be slightly different.

The infants are being followed for 18-22 month outcome and the DSMC will meet on November 4th – at that meeting they will review the available follow-up data.

Would you be available for a call to discuss this sometime today or tomorrow?
Warmest regards,
Rose and cathy

Catherine Y Spong MD
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From: Gantz, Marie
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Confidential FW: NRN Support trial data
Date: Friday, October 30, 2009 12:15:44 PM
Attachments: T1 Patient Description - 30OCT09.doc
Cause of Death - 30OCT09.doc.rtf

The gender difference in the CPAP/surfactant arm has been consistently p=0.06 (it was like that in August when we looked at it and still is). The difference in the oxygen saturation arm is more like p=0.15. The tables with the DR intervention variables are attached, as is information on cause of death.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Das, Abhik
Sent: Friday, October 30, 2009 11:34 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: Confidential FW: NRN Support trial data

It appears that gender differences are not statistically significant for either arm after all the data were in. Marie can address the other question, but there may be some delay because she is also trying to get the final report out to the DSMC.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 30, 2009 8:40 AM
To: Das, Abhik; Gantz, Marie
Subject: Confidential FW: NRN Support trial data

I have been in correspondence with our NICHD and NHLBI leadership for SUPPORT to decide whether or not we have a safety issue that would warrant informing the other dsmc's. Please keep this correspondence confidential for now. I recall that a gender analysis was done - do you have this. Also, Carol is suggesting a cause of death look. Can you send me the table with DR intervention differences in the ventilatory arm?
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Blaisdell, Carol (NIH/NHLBI) [E]

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Sent: Thursday, October 29, 2009 6:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NRN Support trial data

Rose/Cathy ==appreciate your concern, but more analysis may help understand if this is real?
Questions:
What were the (b) (5) [redacted]

In the intent to treat with (b) (5) [redacted]

Given that babies with (b) (5) [redacted]

I seem to recall that area under the curve of (b) (5) [redacted]

How about (b) (5) [redacted]

Carol
Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov<mailto:blaisdellcj@nhlbi.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, October 29, 2009 5:04 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: Confidential NRN Support trial data

Carol and Dorothy-
Thank you for your support for the SUPPORT study. The subcommittee and steering committee met yesterday and today and has some concerns regarding the (b) (5) [redacted]. I am forwarding the primary outcome information and our specific questions for NICHD leadership. I know Carol will be at the dsmc meeting next week.

Your thoughts would be very helpful as there are 3 saturation trials occurring around the world currently. Again- I want to express my thanks

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for all you involvement and spport.

Rose

From: Spong, Catherine (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Oct 29 14:20:53 2009
Subject: NRN Support trial data
Dear Dr. Maddox,

The NRN's SUPPORT trial data analysis for the primary outcome is complete and we want to bring it to your attention. This trial was a factorial design comparing low oxygen vs. high oxygen by two hours of age; the other comparison was CPAP vs. intubation with surfactant in the delivery room. Attached are some slides with data on the primary analyses. (I am sending this email on behalf of Rose who is at the NRN meeting today).

The primary outcome of death or bronchopulmonary dysplasia for the ventilation arm is no difference between CPAP versus intubation with surfactant, but a strong trend and significant secondary outcomes for the CPAP arm, especially in babies born at 24-25 weeks.

For the low vs. high oxygen comparison, there is no difference in the primary outcome of death or ROP. However there is a significant increase in death (predefined secondary outcome) in the lower saturation group (20%) versus the higher saturation group (16%). Offsetting this, is a significantly lower rate of ROP (9%) in the lower saturation group compared to the higher saturation group (18%). This suggests that there is a (b) (5) [redacted]

There are ongoing saturation trials around the world and we are weighing whether we should share the results confidentially (if that is possible) of the significant increase in death with the DSMCs of the ongoing trials. The ongoing trials have a primary outcome of death or neurodevelopmental impairment at 18-22 months. All of these trials recruit infants after birth; the SUPPORT trial consented mothers prior to delivery. Further, gestational age entry criteria may be slightly different.

The infants are being followed for 18-22 month outcome and the DSMC will meet on November 4th - at that meeting they will review the available follow-up data.

Would you be available for a call to discuss this sometime today or tomorrow?
Warmest regards,
Rose and cathy

Catherine Y Spong MD

Chief, Pregnancy and Perinatology Branch

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Table 1. Patient Description for CPAP vs. Surfactant

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P value
GA (weeks)	24-25	43% (285/663)	43% (280/653)	0.9686
	26-27	57% (378/663)	57% (373/653)	
Male		52% (342/663)	57% (370/653)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (254/663)	36% (235/653)	0.3681
	Non-Hispanic White	38% (250/663)	42% (271/653)	
	Hispanic	21% (138/663)	19% (121/653)	
	Other/unknown	3% (21/663)	4% (26/653)	
Birth weight (grams)	Mean (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Apgar at 1 minute <3		23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3		4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)		66% (435/662)	93% (606/652)	<0.0001*
CPAP in the DR (SUPP03)		81% (538/663)	22% (146/653)	<0.0001*
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation		33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)		14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)		5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)		2% (13/660)	4% (27/653)	0.0225*
Antenatal steroids (any)		97% (642/663)	96% (623/652)	0.2248
Antenatal steroids (full course)		74% (486/660)	70% (453/649)	0.1232
Death in the DR (SUPP03/SUPP04)		0% (1/663)	1% (5/653)	0.0978

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Table 1. Patient Description for CPAP vs. Surfactant Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (106/280)	0.0495*
	Non-Hispanic White	32% (92/285)	43% (120/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.3 ± 139.5	0.0713
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1149
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (SUPP03)		73% (207/284)	95% (267/280)	<0.0001*
CPAP in the DR (SUPP03)		72% (205/285)	22% (62/280)	<0.0001*
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
DR intubation for resuscitation		48% (137/284)	31% (87/280)	<0.0001*
Surfactant in DR (SUPP03)		21% (60/284)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		77% (220/284)	99% (276/280)	<0.0001*
Chest compressions in DR (SUPP03)		9% (27/285)	8% (23/280)	0.5982
Epinephrine in DR (SUPP03)		4% (10/285)	5% (15/280)	0.2854
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (SUPP03/SUPP04)		0% (1/285)	1% (4/280)	0.1715

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value*
Male		52% (195/378)	56% (208/373)	0.2511
Race/ethnicity	Non-Hispanic Black	35% (132/378)	35% (129/373)	0.8733
	Non-Hispanic White	42% (158/378)	40% (151/373)	
	Hispanic	20% (75/378)	20% (76/373)	
	Other/unknown	3% (13/378)	5% (17/373)	
Birth weight (grams)	Mean (n=751)	922.2 ± 180.5	921.0 ± 181.4	0.9325
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.9676
Apgar at 1 minute <3		18% (66/377)	22% (83/373)	0.1034
Apgar at 5 minutes <3		2% (7/378)	3% (13/373)	0.1645
PPV in the DR (SUPP03)		60% (228/378)	91% (339/372)	<0.0001*
CPAP in the DR (SUPP03)		88% (333/378)	23% (84/373)	<0.0001*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
DR intubation for resuscitation		21% (78/376)	24% (89/372)	0.2964
Surfactant in DR (SUPP03)		9% (33/376)	50% (186/372)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		59% (223/376)	99% (370/373)	<0.0001*
Chest compressions in DR (SUPP03)		2% (9/375)	5% (17/373)	0.1072
Epinephrine in DR (SUPP03)		1% (3/375)	3% (12/373)	0.0184*
Antenatal steroids (any)		96% (363/378)	94% (352/373)	0.2865
Antenatal steroids (full course)		70% (262/375)	68% (251/371)	0.5146
Death in the DR (SUPP03/SUPP04)		0% (0/378)	0% (1/373)	0.3138

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Table 1. Patient Description for High vs. Low SpO2

Variable	Category	High SpO2 (N=662)	Low SpO2 (N=654)	Unadjusted P-value
GA (weeks)	24-25	44% (289/662)	42% (276/654)	0.5942
	26-27	56% (373/662)	58% (378/654)	
Male		56% (371/662)	52% (341/654)	0.1556
Race/ethnicity	Non-Hispanic Black	35% (232/662)	39% (257/654)	0.2642
	Non-Hispanic White	42% (279/662)	37% (242/654)	
	Hispanic	19% (127/662)	20% (132/654)	
	Other/unknown	4% (24/662)	4% (23/654)	
Birth weight (grams)	Mean (n=1316)	824.8 ± 193.0	835.5 ± 193.4	0.3138
Gestational age at birth (weeks)	Mean (n=1316)	26.1 ± 1.1	26.2 ± 1.1	0.3925
Apgar at 1 minute <3		26% (169/662)	23% (152/652)	0.3500
Apgar at 5 minutes <3		4% (24/662)	5% (34/654)	0.1644
PPV in the DR (SUPP03)		80% (532/661)	78% (509/653)	0.2572
CPAP in the DR (SUPP03)		52% (345/662)	52% (339/654)	0.9190
Intubated in DR (SUPP03)		65% (432/660)	62% (404/652)	0.1885
DR intubation for resuscitation		30% (197/660)	30% (194/652)	0.9703
Surfactant in DR (SUPP03)		34% (227/660)	31% (201/652)	0.1684
Surfactant in DR or NICU (SUPP03, SUPP04)		85% (558/660)	81% (531/653)	0.1200
Chest compressions in DR (SUPP03)		6% (38/662)	6% (38/651)	0.9400
Epinephrine in DR (SUPP03)		3% (21/662)	3% (19/651)	0.7892
Antenatal steroids (any)		96% (632/661)	97% (633/654)	0.2648
Antenatal steroids (full course)		70% (462/658)	73% (477/651)	0.2191
Death in the DR (SUPP03/SUPP04)		0% (3/662)	0% (3/654)	0.9881

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Table 1 Patient Description for High vs. Low SpO2
Where GA is 24-25 weeks

Characteristic	Category	High SpO2 (N=289)	Low SpO2 (N=276)	Unadjusted P-value
Male		59% (170/289)	50% (139/276)	0.0434*
Race/ethnicity	Non-Hispanic Black	37% (107/289)	44% (121/276)	0.0974
	Non-Hispanic White	41% (118/289)	34% (94/276)	
	Hispanic	18% (52/289)	20% (56/276)	
	Other/unknown	4% (12/289)	2% (5/276)	
Birth weight (grams)	Mean (n=565)	711.5 ± 133.7	705.3 ± 131.4	0.5838
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.1 ± 0.6	0.5518
Apgar at 1 minute <3		30% (87/289)	31% (85/275)	0.8355
Apgar at 5 minutes <3		6% (16/289)	8% (22/276)	0.2481
PPV in the DR (SUPP03)		86% (247/288)	82% (227/276)	0.2542
CPAP in the DR (SUPP03)		49% (141/289)	46% (126/276)	0.4554
Intubated in DR (SUPP03)		75% (216/288)	70% (192/276)	0.1492
DR intubation for resuscitation		41% (117/288)	39% (107/276)	0.6523
Surfactant in DR (SUPP03)		40% (115/288)	34% (94/276)	0.1489
Surfactant in DR or NICU (SUPP03, SUPP04)		91% (261/288)	85% (235/276)	0.0457*
Chest compressions in DR (SUPP03)		9% (26/289)	9% (24/276)	0.8998
Epinephrine in DR (SUPP03)		6% (16/289)	3% (9/276)	0.1886
Antenatal steroids (any)		97% (279/288)	98% (271/276)	0.3163
Antenatal steroids (full course)		74% (213/287)	77% (213/276)	0.4136
Death in the DR (SUPP03/SUPP04)		1% (3/289)	1% (2/276)	0.6909

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Table 1 Patient Description for High vs. Low SpO2
Where GA is 26-27 weeks

Characteristic	Category	High SpO2 (N=375)	Low SpO2 (N=378)	Unadjusted P value
Male		54% (201/373)	53% (202/378)	0.9020
Race/ethnicity	Non-Hispanic Black	34% (125/373)	36% (136/378)	0.5351
	Non-Hispanic White	43% (161/373)	39% (148/378)	
	Hispanic	20% (75/373)	20% (76/378)	
	Other/unknown	3% (12/373)	5% (18/378)	
Birth weight (grams)	Mean (n=751)	912.6 ± 186.1	930.5 ± 175.2	0.1733
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.6046
Apgar at 1 minute <3		22% (82/373)	18% (67/377)	0.1483
Apgar at 5 minutes <3		2% (8/373)	3% (12/378)	0.3808
PPV in the DR (SUPP03)		76% (285/373)	75% (282/377)	0.6085
CPAP in the DR (SUPP03)		55% (204/373)	56% (213/378)	0.6477
Intubated in DR (SUPP03)		58% (216/372)	56% (212/376)	0.6421
DR intubation for resuscitation		22% (80/372)	23% (87/376)	0.5918
Surfactant in DR (SUPP03)		30% (112/372)	28% (107/376)	0.6200
Surfactant in DR or NICU (SUPP03, SUPP04)		80% (297/372)	79% (296/377)	0.6555
Chest compressions in DR (SUPP03)		3% (12/373)	4% (14/375)	0.7000
Epinephrine in DR (SUPP03)		1% (5/373)	3% (10/375)	0.1958
Antenatal steroids (any)		95% (353/373)	96% (362/378)	0.4689
Antenatal steroids (full course)		67% (249/371)	70% (264/375)	0.3332
Death in the DR (SUPP03/SUPP04)		0% (0/373)	0% (1/378)	0.3202

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Cause of Death for CPAP vs. Surfactant

Variable	Category	CPAP (N=109)	Surfactant (N=128)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	20% (22/109)	31% (40/128)
	2=BPD	11% (12/109)	9% (12/128)
	3=Infection	24% (26/109)	16% (20/128)
	4=NEC	13% (14/109)	18% (23/128)
	5=CNS Insult	12% (13/109)	6% (8/128)
	6=Immaturity	4% (4/109)	5% (6/128)
	7=Other	17% (18/109)	15% (19/128)

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Cause of Death for CPAP vs. Surfactant
Where GA is 24-25 weeks

Variable	Category	CPAP (N=68)	Surfactant (N=90)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	19% (13/68)	34% (31/90)
	2=BPD	15% (10/68)	8% (7/90)
	3=Infection	21% (14/68)	17% (15/90)
	4=NEC	15% (10/68)	18% (16/90)
	5=CNS Insult	16% (11/68)	6% (5/90)
	6=Immaturity	4% (3/68)	6% (5/90)
	7=Other	10% (7/68)	12% (11/90)

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Cause of Death for CPAP vs. Surfactant
Where GA is 26-27 weeks

Variable	Category	CPAP (N=41)	Surfactant (N=38)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	22% (9/41)	24% (9/38)
	2=BPD	5% (2/41)	13% (5/38)
	3=Infection	29% (12/41)	13% (5/38)
	4=NEC	10% (4/41)	18% (7/38)
	5=CNS Insult	5% (2/41)	8% (3/38)
	6=Immaturity	2% (1/41)	3% (1/38)
	7=Other	27% (11/41)	21% (8/38)

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Cause of Death for High vs. Low SpO2

Variable	Category	High SpO2 (N=107)	Low SpO2 (N=130)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	29% (31/107)	24% (31/130)
	2=BPD	9% (10/107)	11% (14/130)
	3=Infection	20% (21/107)	19% (25/130)
	4=NEC	13% (14/107)	18% (23/130)
	5=CNS Insult	8% (9/107)	9% (12/130)
	6=Immaturity	3% (3/107)	5% (7/130)
	7=Other	18% (19/107)	14% (18/130)

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Cause of Death for High vs. Low SpO2
Where GA is 24-25 weeks

Variable	Category	High SpO2 (N=73)	Low SpO2 (N=85)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	29% (21/73)	27% (23/85)
	2=BPD	12% (9/73)	9% (8/85)
	3=Infection	18% (13/73)	19% (16/85)
	4=NEC	12% (9/73)	20% (17/85)
	5=CNS Insult	8% (6/73)	12% (10/85)
	6=Immaturity	4% (3/73)	6% (5/85)
	7=Other	16% (12/73)	7% (6/85)

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Cause of Death for High vs. Low SpO2
Where GA is 26-27 weeks

Variable	Category	High SpO2 (N=34)	Low SpO2 (N=45)
Contributory cause of death (NG03e, NG03, NG05)	1=RDS	29% (10/34)	18% (8/45)
	2=BPD	3% (1/34)	13% (6/45)
	3=Infection	24% (8/34)	20% (9/45)
	4=NEC	15% (5/34)	13% (6/45)
	5=CNS Insult	9% (3/34)	4% (2/45)
	6=Immaturity	0% (0/34)	4% (2/45)
	7=Other	21% (7/34)	27% (12/45)

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"Other" causes of death specified by current classification in COD table

Contributory cause of death (NG03e, NG03, NG05)=1=RDS

Obs	Other COD specified on NG03e, NG03 or NG05
1	extreme prematurity, RDS, suspected sepsis

Contributory cause of death (NG03e, NG03, NG05)=2=BPD

Obs	Other COD specified on NG03e, NG03 or NG05
2	bpd with multi-systaem organ failure,developed abd. compartment syndrome post-op stricture repair
3	Early onset sepsis & BPD w/severe intracranial hemorrhage.
4	PAHN, Liver Failure, CLD, Resp Failure
5	Endocarditis, Staph pneumonia, multiple pneumothoraces, cystic abscess in lung and advanced BPD
6	Cardiopulmonary arrest due to Pulmonary hypertension & Systemic hypotension & chronic lung disease

Contributory cause of death (NG03e, NG03, NG05)=3=Infection

Obs	Other COD specified on NG03e, NG03 or NG05
7	disseminated Candidiasis
8	pneumonia, sepsis (Blood and lung cultures (+) for S. Aureus, E. Cloacae)
9	proven NEC, sepsis, extreme prematurity
10	extreme prematurity, suspected pulmonary hypoplasia, pneumonia, presumed sepsis
11	ELBW, acute renal failure, severe lung disease, pneumonia, proven sepsis, hypocalcemia
12	septic shock, cardio-respiratory failure, renal failure
13	extreme prematurity, and sepsis
14	extreme prematurity, ecoli sepsis,meningitis
15	Pseudomonas sepsis, acute resp. failure, renal failure
16	pulmonary hypoplasia, clinical sepsis
17	suspected sepsis, DIC, and cerebellar hemorrhage
18	bilateral chylothoraces, sepsis, meconium peritonitis

Contributory cause of death (NG03e, NG03, NG05)=5=CNS Insult

Obs	Other COD specified on NG03e, NG03 or NG05
19	Severe IVH, Pulmonary hemorrhage, HMD, PIE
20	Severe IVH and Pulmonary Hemorrhage
21	Pulmonary hypoplasia with severe intraparenchymal IVH
22	Renal failure and Intraventricular hemorrhage

Contributory cause of death (NG03e, NG03, NG05)=6=Immaturity

Obs	Other COD specified on NG03e, NG03 or NG05
23	severe IUGR
24	prematurity, pulmonary hypertension,cardiorespiratory failure
25	extreme prematurity, severe pulmonary insufficiency

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"Other" causes of death specified by current classification in COD table

Contributory cause of death (NG03e, NG03, NG05)=7=Other

Obs	Other COD specified on NG03e, NG03 or NG05
26	extensive hemorrhage mid brain,brain stem,thalamic with uncal herniation and hydrocephaly
27	Respiratory failure
28	Pulmonary hemorrhage
29	liver failure
30	renal failure; DIC
31	liver failure with bleeding; ost. sites
32	PPHN-persistent pulmonary hypertension of neonate
33	intravascular hemorrhage before birth
34	per autopsy cause is exsanguination
35	pulmonary hypertension, pulmonary hypoplasia
36	pulmonary hypoplasia, chroramnionitis
37	Pulmonary Hypoplasia
38	twin to twin transfusion syndrome
39	massive pulmonary hemorrhage
40	pulmonary hemorrhage
41	pulmonary hypoplasia
42	Lung hypoplasia
43	hypoplastic lung syndrome due to pprom
44	Massive pulmonary hemorrhage without RDS
45	pulmonary hypoplasia due to multiple congenital anomalies
46	MULTI SYSTEM ORGAN FAILURE
47	severe hypoplastic lungs
48	renal failure;
49	severe pulmonary hypertension
50	tetralogy of fallot 7 other multiple cardiac anomalies renal anomalies(possiblby va cterl syndrome
51	cardiac arrythmia
52	extensive hemorrhage of rt. chest cavity after chest tube placement
53	perforation of right atrium by tip of PICC line
54	transposition of the great vessels
55	PREMATURITY, PULMONARY HYPOPLESIA, EXOPHAGEAL ATRESIA, SKELETAL ANNOMALIES
56	probable pulmonary hypoplasia

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Vote: Authorship
Date: Friday, October 30, 2009 9:22:13 AM

Hi Rose:

I vote for absolute N recruited.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 30, 2009 8:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; cunningham@rti.org; (kzaterka@rti.org); Petrie, Carolyn
Subject: Vote: Authorship

Hi,

In follow up to yesterday's publication discussion, please send me your vote by November 3 for NRN Primary study manuscripts for author order following subcommittee members:

1._____ Leave as is (50% credit for absolute number recruited and 50% credit for enrolled/eligible)

2.__x___ Change to absolute number recruited

3._____ Change to a combination of absolute number and percent enrolled/eligible (AND SEND YOUR PROPOSAL WITH YOUR VOTE)

Rosemary D. Higgins, MD

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Program Scientist for the NICHD Neonatal Research Network

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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT authorship
Date: Thursday, October 29, 2009 10:57:15 PM
Attachments: Attach0.html

Rose

See correspondence below

Both Susie Buchter and Anthony Plazza at Emory worked on SUPPORT. I would propose that Susie be an author on the CPAP /vent paper and that Anthony be an authore on the O2 sat paper-- They will of course review and comment on the papers

THANKS

BJS

----- Original Message -----

I would like to be on the CPAP/vent paper, but would be pleased for Anthony to be on sat paper.
Thanks for including us both.
SB

Sent via BlackBerry by AT&T

From: Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>
Date: Thu, 29 Oct 2009 10:56:12 -0400
To: Buchter, Susie<dbuchte@emory.edu>; Susie Buchter<Susie.Buchter@oz.ped.emory.edu>
Subject: SUPPORT

There will be 2 primary papers from SUPPORT-- a CPAP/vent paper and a sat paper
Although I named you as the Emory PI on the paper, Anthony was a very strong collaborator. Are you OK with my asking the NRN to have you as the Emory author on one paper and Anthony on the other?
BJS

Barbara J. Stoll, MD

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George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
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I would like to be on the CPAP/vent paper, but would be pleased for Anthony to be on sat paper. Thanks for including us both.
SB

Sent via BlackBerry by AT&T

From: Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>
Date: Thu, 29 Oct 2009 10:56:12 -0400
To: Buchter, Susie<dbuchte@emory.edu>; Susie Buchter<Susie.Buchter@oz.ped.emory.edu>
Subject: SUPPORT

There will be 2 primary papers from SUPPORT-- a CPAP/vent paper and a sat paper Although I named you as the Emory PI on the paper, Anthony was a very strong collaborator. Are you OK with my asking the NRN to have you as the Emory author on one paper and Anthony on the other?
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Clinical trials.gov
Date: Thursday, October 29, 2009 11:06:45 AM

The ROP outcome for SUPPoRT says 36 weeks. This is not correct - it is 55 weeks as per the manual - please chnage this

Thanks
Rose

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Rich, Wade
Subject: Steering Comm Preserntation
Date: Thursday, October 29, 2009 9:41:25 AM
Attachments: SUPPORT outcomes 10-29-09.ppt
T3 BPD Outcomes - 27OCT09.doc
T1 Patient Description - 27OCT09.doc
T2 Other Outcomes - 27OCT09.doc

Hi Rose
I made a few changes. Can you show this during the meeting.
Also can Marie or you have the Tables of Results that Marie had done - ie I have attached – I think if there are questions we should show these
Thanks
I'm here and ready
Neil

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SUPPORT Outcomes: Ventilation Arm

Outcome	CPAP (N=663)	Surfactant (N=653)	Adjusted P-value
Death in hospital	16% (109/663)	20% (128/653)	0.126
Death @36wks PMA	14% (94/663)	17% (114/653)	0.089
BPD (Phys Def) or Death @36wks	48% (317/663)	51% (333/653)	0.304
BPD (Oxygen) or Death @36 wks	49% (322/663)	54% (353/653)	0.062

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Ventilation Arm Outcomes by GA

GA 24-25 weeks	CPAP (N=285)	Surfactant (N=280)	Adjusted P-value
Death in hospital	24% (68/285)	32% (90/280)	0.034

GA 26-27 weeks	CPAP (N=378)	Surfactant (N=373)	Adjusted P-value
Death in hospital	11% (41/378)	10% (38/373)	0.797

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SUPPORT Conclusions: Ventilation Arm

- ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a protocol limited ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a lower incidence of death or survival with BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcomes.
- Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants.

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SUPPORT Outcomes: SpO2 Arm

Outcome	Low SpO2 (N=654)	High SpO2 (N=662)	Adjusted P-value
Death in hospital	20% (130/654)	16% (107/662)	0.041
ROP	9% (43/483)	18% (95/514)	<0.001
ROP or Death in hospital	28% (171/605)	32% (198/616)	0.205

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SUPPORT Conclusions: SpO2 Arm

- In the current trial, lower oxygen saturation targeting (actual 85-89%) resulted in a 4% increased mortality and a decrease in Threshold ROP of 9%.
- It is interesting and worrisome that the combined risk difference observed in the trials from the1950s using restricted oxygen was a 4.9% increase in mortality in the oxygen restricted group, which is very similar to the 4% mortality seen in our lower targeted SpO2.

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Table 3. BPD outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs. Surfactant (95% CI)
Death at any time while hospitalized	16% (109/663)	20% (128/653)	0.84 (0.67, 1.05)
Death by 36 weeks PMA	14% (94/663)	17% (114/653)	0.81 (0.63, 1.03)
BPD (physiologic definition)	39% (223/569)	41% (219/539)	0.99 (0.87, 1.14)
BPD (physiologic definition) or death by 36 weeks PMA	48% (317/663)	51% (333/653)	0.95 (0.85, 1.05)
BPD (supplemental O2)	40% (228/569)	44% (239/539)	0.93 (0.82, 1.06)
BPD (supplemental O2) or death by 36 weeks PMA	49% (322/663)	54% (353/653)	0.91 (0.82, 1)
ROP	14% (70/517)	14% (68/480)	0.95 (0.7, 1.28)
ROP or death	28% (176/620)	32% (193/601)	0.87 (0.74, 1.03)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3. BPD outcomes for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)
Death at any time while hospitalized	24% (68/285)	32% (90/280)	0.74 (0.57, 0.98)
Death by 36 weeks PMA	20% (57/285)	29% (82/280)	0.68 (0.5, 0.92)
BPD (physiologic definition)	55% (125/228)	55% (108/198)	1.06 (0.91, 1.25)
BPD (physiologic definition) or death by 36 weeks PMA	64% (182/285)	68% (190/280)	0.96 (0.85, 1.07)
BPD (supplemental O2)	54% (122/228)	54% (106/198)	1.05 (0.9, 1.23)
BPD (supplemental O2) or death by 36 weeks PMA	63% (179/285)	67% (188/280)	0.95 (0.84, 1.06)
ROP	23% (47/202)	31% (55/175)	0.75 (0.54, 1.05)
ROP or death	42% (112/266)	55% (144/261)	0.74 (0.62, 0.89)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3. BPD outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)
Death at any time while hospitalized	11% (41/378)	10% (38/373)	1.06 (0.7, 1.6)
Death by 36 weeks PMA	10% (37/378)	9% (32/373)	1.12 (0.72, 1.75)
BPD (physiologic definition)	29% (98/341)	33% (111/341)	0.92 (0.74, 1.15)
BPD (physiologic definition) or death by 36 weeks PMA	36% (135/378)	38% (143/373)	0.94 (0.78, 1.13)
BPD (supplemental O2)	31% (106/341)	39% (133/341)	0.83 (0.68, 1.01)
BPD (supplemental O2) or death by 36 weeks PMA	38% (143/378)	44% (165/373)	0.87 (0.73, 1.03)
ROP	7% (23/315)	4% (13/305)	1.86 (0.94, 3.67)
ROP or death	18% (64/354)	14% (49/340)	1.25 (0.88, 1.77)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 1 Patient Description for CPAP vs. Surfactant

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43% (285/663)	43% (280/653)	0.9686
	26-27	57% (378/663)	57% (373/653)	
Male		52% (342/663)	57% (370/653)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (254/663)	36% (235/653)	0.3681
	Non-Hispanic White	38% (250/663)	42% (271/653)	
	Hispanic	21% (138/663)	19% (121/653)	
	Other/unknown	3% (21/663)	4% (26/653)	
Birth weight (grams)	Mean (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Apgar at 1 minute <3		23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3		4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)		66% (435/662)	93% (606/652)	<0.0001*
CPAP in the DR (SUPP03)		81% (538/663)	22% (146/653)	<0.0001*
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation		33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)		14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)		5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)		2% (13/660)	4% (27/653)	0.0225*
Antenatal steroids (any)		97% (642/663)	96% (623/652)	0.2248
Antenatal steroids (full course)		74% (486/660)	70% (453/649)	0.1232
Death in the DR (SUPP03/SUPP04)		0% (1/663)	1% (5/653)	0.0978

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Table 1 Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (106/280)	0.0495*
	Non-Hispanic White	32% (92/285)	43% (120/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.3 ± 139.5	0.0713
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1149
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (SUPP03)		73% (207/284)	95% (267/280)	<0.0001*
CPAP in the DR (SUPP03)		72% (205/285)	22% (62/280)	<0.0001*
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
DR intubation for resuscitation		48% (137/284)	31% (87/280)	<0.0001*
Surfactant in DR (SUPP03)		21% (60/284)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		77% (220/284)	99% (276/280)	<0.0001*
Chest compressions in DR (SUPP03)		9% (27/285)	8% (23/280)	0.5982
Epinephrine in DR (SUPP03)		4% (10/285)	5% (15/280)	0.2854
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (SUPP03/SUPP04)		0% (1/285)	1% (4/280)	0.1715

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Table 1 Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Male		52% (195/378)	56% (208/373)	0.2511
Race/ethnicity	Non-Hispanic Black	35% (132/378)	35% (129/373)	0.8733
	Non-Hispanic White	42% (158/378)	40% (151/373)	
	Hispanic	20% (75/378)	20% (76/373)	
	Other/unknown	3% (13/378)	5% (17/373)	
Birth weight (grams)	Mean (n=751)	922.2 ± 180.5	921.0 ± 181.4	0.9325
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.9676
Apgar at 1 minute <3		18% (66/377)	22% (83/373)	0.1034
Apgar at 5 minutes <3		2% (7/378)	3% (13/373)	0.1645
PPV in the DR (SUPP03)		60% (228/378)	91% (339/372)	<0.0001*
CPAP in the DR (SUPP03)		88% (333/378)	23% (84/373)	<0.0001*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
DR intubation for resuscitation		21% (78/376)	24% (89/372)	0.2964
Surfactant in DR (SUPP03)		9% (33/376)	50% (186/372)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		59% (223/376)	99% (370/373)	<0.0001*
Chest compressions in DR (SUPP03)		2% (9/375)	5% (17/373)	0.1072
Epinephrine in DR (SUPP03)		1% (3/375)	3% (12/373)	0.0184*
Antenatal steroids (any)		96% (363/378)	94% (352/373)	0.2865
Antenatal steroids (full course)		70% (262/375)	68% (251/371)	0.5146
Death in the DR (SUPP03/SUPP04)		0% (0/378)	0% (1/373)	0.3138

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Table 2: Other outcomes for CPAP vs. Surfactant

Characteristic	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
Death in the first week		6% (40/663)	6% (39/653)	0.9630
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=1075)	100.4 ± 42.9	101.4 ± 41.6	0.7047
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=1079)	97.7 ± 43.4	97.0 ± 41.6	0.7883
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=1098)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=1098)	20.0 ± 23.9	23.2 ± 26.2	0.0331*
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=1082)	53.6 ± 21.7	55.1 ± 20.3	0.2346
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=1098)	16.1 ± 13.1	15.8 ± 14.7	0.7516
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=1098)	3.5 ± 6.9	3.6 ± 7.1	0.7239
Discharge on oxygen (NG03 or NG05)		22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		55% (362/655)	49% (318/652)	0.0188*
Pneumothorax (NG03 or SUPP08)		8% (54/663)	6% (36/653)	0.0586
Any air leak in first 14 days (SUPP08)		7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC (NG03)		13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery (NG03)		11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4 (NG03)		14% (92/642)	11% (72/628)	0.1279
PVL (NG03 or MRI01)		4% (28/643)	4% (26/629)	0.8450
Death or PVL (NG03 or MRI01)		20% (134/663)	23% (147/653)	0.3086
Postnatal steroids for BPD (NG03)		7% (47/649)	13% (83/631)	0.0005*
Postnatal steroids after DOL 21 (SUPP09)		17% (114/659)	23% (149/652)	0.012*
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		77% (508/661)	100% (649/652)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		83% (551/663)	100% (651/653)	<0.0001*

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Table 2. Other outcomes for CPAP vs. Surfactant Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week		9% (25/285)	10% (29/280)	0.5217
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=405)	120.7 ± 47.9	119.2 ± 40.5	0.7394
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=407)	117.6 ± 47.1	116.8 ± 43.3	0.8579
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=421)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=421)	33.1 ± 27.3	37.5 ± 29.0	0.1138
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=421)	66.5 ± 16.8	67.6 ± 16.2	0.5026
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=421)	18.4 ± 13.8	17.7 ± 16.1	0.5998
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=421)	5.2 ± 8.2	5.5 ± 8.6	0.7016
Discharge on oxygen (NG03 or NG05)		32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		34% (97/283)	26% (74/280)	0.0429*
Pneumothorax (NG03 or SUPP08)		10% (29/285)	8% (21/280)	0.2629
Any air leak in first 14 days (SUPP08)		8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC (NG03)		15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery (NG03)		16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4 (NG03)		20% (54/273)	17% (45/265)	0.4022
PVL (NG03 or MRI01)		6% (17/273)	5% (14/265)	0.6385
Death or PVL (NG03 or MRI01)		29% (83/285)	36% (100/280)	0.0941
Postnatal steroids for BPD (NG03)		13% (36/276)	20% (54/264)	0.0209*
Postnatal steroids after DOL 21 (SUPP09)		28% (78/282)	34% (94/279)	0.1213
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		88% (250/285)	99% (278/280)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		94% (267/285)	100% (279/280)	0.0001*

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Table 2. Other outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Death in the first week		4% (15/378)	3% (10/373)	0.3255
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=670)	87.5 ± 33.5	91.3 ± 38.8	0.1699
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=672)	85.0 ± 35.4	85.9 ± 36.2	0.7477
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=677)	40.6 ± 32.6	47.1 ± 35.1	0.0126*
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=677)	11.3 ± 16.3	14.9 ± 20.3	0.0122*
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=661)	44.7 ± 20.2	47.7 ± 18.8	0.0555
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=677)	14.6 ± 12.5	14.8 ± 13.8	0.8425
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=677)	2.3 ± 5.6	2.5 ± 5.8	0.6778
Discharge on oxygen (NG03 or NG05)		16% (53/336)	20% (65/331)	0.1911
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		71% (265/372)	66% (244/372)	0.0977
Pneumothorax (NG03 or SUPP08)		7% (25/378)	4% (15/373)	0.1137
Any air leak in first 14 days (SUPP08)		6% (22/378)	6% (21/373)	0.9107
Medical or surgical NEC (NG03)		11% (41/375)	8% (28/368)	0.1185
PDA requiring surgery (NG03)		7% (27/374)	6% (22/368)	0.4962
IVH grade 3-4 (NG03)		10% (38/369)	7% (27/363)	0.1738
PVL (NG03 or MRI01)		3% (11/370)	3% (12/364)	0.8013
Death or PVL (NG03 or MRI01)		13% (51/378)	13% (47/373)	0.7169
Postnatal steroids for BPD (NG03)		3% (11/373)	8% (29/367)	0.0029*
Postnatal steroids after DOL 21 (SUPP09)		10% (36/377)	15% (55/373)	0.0293*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		69% (258/376)	100% (371/372)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		75% (284/378)	100% (372/373)	<0.0001*

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; Finer, Neil
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: SUPPORT slides
Date: Wednesday, October 28, 2009 7:55:22 PM
Attachments: SUPPORT outcomes 10-28-09.ppt

Here are a few slides for tomorrow highlighting the SUPPORT outcomes and conclusions from each treatment arm.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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SUPPORT Outcomes: Ventilation Arm

Outcome	CPAP (N=663)	Surfactant (N=653)	Adjusted P-value
Death in hospital	16% (109/663)	20% (128/653)	0.126
Death @36wks PMA	14% (94/663)	17% (114/653)	0.089
BPD (Phys Def) or Death @36wks	48% (317/663)	51% (333/653)	0.304
BPD (Oxygen) or Death @36 wks	49% (322/663)	54% (353/653)	0.062

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Ventilation Arm Outcomes by GA

GA 24-25 weeks	CPAP (N=285)	Surfactant (N=280)	Adjusted P-value
Death in hospital	24% (68/285)	32% (90/280)	0.034

GA 26-27 weeks	CPAP (N=378)	Surfactant (N=373)	Adjusted P-value
Death in hospital	11% (41/378)	10% (38/373)	0.797

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SUPPORT Conclusions: Ventilation Arm

- ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PMA with no demonstrable increase in any adverse neonatal outcomes.
- Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants.

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SUPPORT Outcomes: SpO2 Arm

Outcome	Low SpO2 (N=654)	High SpO2 (N=662)	Adjusted P-value
Death in hospital	20% (130/654)	16% (107/662)	0.041
ROP	9% (43/483)	18% (95/514)	<0.001
ROP or Death in hospital	28% (171/605)	32% (198/616)	0.205

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SUPPORT Conclusions: SpO2 Arm

- In the current trial, lower oxygen saturation targeting (actual 85-89%) resulted in an increased risk of mortality.
- It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group, which is very similar to the 4% mortality increase in the lower targeted SpO2 group that was observed in our trial.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rogers, Christine (NIH/OD) [E]
Subject: Re:
Date: Wednesday, October 28, 2009 8:23:11 AM

Print as is

Also- when you come over, please give the documents directly to me - they are confidential

Thanks
Rose

----- Original Message -----
From: Rogers, Christine (NIH/OD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Oct 28 08:18:49 2009
Subject: RE:

Rose,
Do you want me to accept the changes, or print the document showing the mark ups (Support CPAP vs Surf)?

Is double sided ok for all?

Thanks,
Christie

Christine M. Rogers
Extramural Support Assistant
Division of Extramural Activities Support
Eunice Kennedy Shriver National Institute of Child Health and Development
6100 Executive Blvd., Room 4B03 MSC 7510
Bethesda, MD 20852
(For overnight delivery use Rockville, MD 20592)
Phone: 301-435-6907
Fax: 301-496-3790
E-mail: rogerscm@mail.nih.gov
NICHD Website: www.nichd.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, October 28, 2009 6:49 AM
To: Rogers, Christine (NIH/OD) [E]
Subject: Fw:

15 of each

Thanks
Rose

----- Original Message -----
From: Gantz, Marie <mgantz@rti.org>
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu <WCarlo@PEDS.UAB.edu>; Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>

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Sent: Tue Oct 27 19:58:40 2009
Subject: RE:

Here are the new results for the CPAP-Surf paper. I have made edits to the text to reflect the new numbers (which are almost the same as the old ones).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 27, 2009 7:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Yes Please

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 27, 2009 2:56 PM
To: Gantz, Marie; Finer, Neil
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Marie
Thanks

Neil - shall we get copies for the subcommittee meeting??
Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Gantz, Marie [mgantz@rti.org]
Sent: Tuesday, October 27, 2009 5:05 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Attached is Table 2 for Wally's paper which now includes the ROP/death outcome. FYI, we have the outcome for 93% of SUPPORT infants. You will note that our N is 1316 - we found out this week that for one of our withdrawn patients we needed to exclude all data (like we did for the patient withdrawn from UCSD).

I will send the CPAP-Surfactant tables soon.

Marie

Marie Gantz, Ph.D.
Research Statistician

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RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 26, 2009 2:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik
Subject:

Hello Everyone
I am querying you to determine if we will have enough time to redo all the CPAP-Surf Tables and data with the final data before the meeting on Wednesday. I would like to get the committee's input on that manuscript and get it in final shape. I obviously also want to know when we will see the final ROP data set for the SpO2 paper. These questions are key regarding our agenda on Wednesday.
Please let me know where we are?
We are also awaiting the final data etc to finalize the Consent paper.
I would like to get this into submission as soon as we can
I look forward to hearing from you.
Neil

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Re:
Date: Tuesday, October 27, 2009 8:53:42 PM

Thanks Rose
I hope the [redacted]
Talk to you tomorrow
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 27, 2009 4:35 PM
To: Finer, Neil
Subject: Re:

Neil
I am sorry to hear [redacted]

Talk to you tomorrow

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Gantz, Marie <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>
Cc: adas@rti.org <adas@rti.org>; kzaterka@rti.org <kzaterka@rti.org>; WCarlo@PEDS.UAB.edu <WCarlo@PEDS.UAB.edu>; Rich, Wade <wrich@ucsd.edu>
Sent: Tue Oct 27 19:28:23 2009
Subject: RE:

Marie
Any idea why we have more missing outcomes in the Hi SpO2 Group?
In addition are we going to run analyses making assumptions that all the missing data either did have or did not have ROP? I assume that we will need to do this especially as the lower SpO2 group with more death has less ROP without such an adjustment - The missing infants are about 20% of the total
It is again interesting that BPD by oxygen is significantly affected whereas the Physiologic is not - consistent.
Lots to think about. I will wait for the SURF-CPAP data
I will talk to you tomorrow - I am on service but will ensure that I am available - I also have [redacted] but I think these results are even a bigger pain
Be well and Thanks
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 27, 2009 4:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Finer, Neil
Cc: adas@rti.org; kzaterka@rti.org
Subject: RE:

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Yes, ROP/death is as specified in the protocol: threshold ROP or need for surgery (I included Avastin) vs. mature eyes or two exams with vessels in zone III. Death is death while hospitalized.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 27, 2009 7:11 PM
To: 'wcarlo@peds.uab.edu'; Gantz, Marie; 'nfiner@ucsd.edu'
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: Re:

My take is yes - no difference. The secondary outcomes show benefor with rop and bpd at the expense of a higer death rate. Similar to phototherapy in the small strata!

Rose

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Gantz, Marie <mgantz@rti.org>; Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu <WCarlo@PEDS.UAB.edu>; Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tue Oct 27 19:09:25 2009
Subject: RE:

Marie.

Does ROP/death in the table refer to the primary outcome as specified in the protocol?

Wally

-----Original Message-----
From: Gantz, Marie <mgantz@rti.org>
Sent: Tuesday, October 27, 2009 4:06 PM
To: Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Cc: WCarlo@PEDS.UAB.edu <WCarlo@PEDS.UAB.edu>; Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>
Subject: RE:

Attached is Table 2 for Wally's paper which now includes the ROP/death outcome. FYI, we have the outcome for 93% of SUPPORT infants. You will note that our N is 1316 - we found out this week that for one of our withdrawn patients we needed to exclude all data (like we did for the patient withdrawn from UCSD).

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I will send the CPAP-Surfactant tables soon.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 26, 2009 2:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik
Subject:

Hello Everyone

I am querying you to determine if we will have enough time to redo all the CPAP-Surf Tables and data with the final data before the meeting on Wednesday. I would like to get the committee's input on that manuscript and get it in final shape. I obviously also want to know when we will see the final ROP data set for the SpO2 paper. These questions are key regarding our agenda on Wednesday.

Please let me know where we are?

We are also awaiting the final data etc to finalize the Consent paper. I would like to get this into submission as soon as we can

I look forward to hearing from you.

Neil

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From: Finer, Neil
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin; Rich, Wade
Subject: RE:
Date: Tuesday, October 27, 2009 8:51:29 PM
Attachments: SUPPORT CPAP vs Surf Oct 27 09Rev NF doc.rtf

Thanks Marie
Can you insert all the p values as adjusted only - I see no point to having unadjusted anywhere as we say in the methods that we will do such adjustments
If you have time please make these changes and remove all the remaining comments - yours I think, and then circulate to the subcommittee for our meeting- It makes for easier reading if all the changes are accepted.
Thanks
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 27, 2009 4:59 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Here are the new results for the CPAP-Surf paper. I have made edits to the text to reflect the new numbers (which are almost the same as the old ones).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 27, 2009 7:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Yes Please

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 27, 2009 2:56 PM
To: Gantz, Marie; Finer, Neil
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Marie
Thanks

Neil - shall we get copies for the subcommittee meeting??
Rose

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Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Gantz, Marie [mgantz@rti.org]
Sent: Tuesday, October 27, 2009 5:05 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

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Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
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Sent: Monday, October 26, 2009 2:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik
Subject:

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Please let me know where we are?
We are also awaiting the final data etc to finalize the Consent paper.
I would like to get this into submission as soon as we can
I look forward to hearing from you.
Neil

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Address correspondence to

Neil Finer, MD

402 Dickenson St, 8774

San Diego, Ca, 92103-8774

Email – nfiner@ucsd.edu

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of consenting parents of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP or surfactant; those randomized to CPAP had CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings and infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1316 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group in the delivery room (all p<0.001), and 67% of the CPAP infants received surfactant in either the delivery room or NICU. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98). There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019) and fewer required post natal steroids for BPD, (p<.001). All infants in the Surfactant arm were intubated, compared with only ~~83~~77% of the CPAP infants requiring intubation during their nursery course, (p<0.001). There were no significant differences between the groups for air leaks including pneumothoraces.

Comment [MG1]: Unadjusted

Comment [MG2]: Unadjusted

Comment [MG3]: Unadjusted

Comment [MG4]: 77% were intubated in the DR or NICU

Comment [MG5]: Unadjusted

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Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so

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for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[44], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of

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clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

Results:

There were 1316 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; 67% of the CPAP infants received surfactant in the delivery room or NICU, compared to 99% of those in the surfactant group (all p<0.0001). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, p<0.0001, Table 2.

Comment [MG6]: Unadjusted

Comment [MG7]: Unadjusted

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 49% versus 54%, (RR 0.91, 05% CI 0.82, 1.00, when adjusted for gestational age, center and familial clustering as prespecified). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (39% vs 41%, RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, or discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required

Comment [MG8]: If you want oxygen on the day of discharge, that is different and I can get those numbers for you, but what is in the table is discharge on oxygen.

Comment [MG9]: Unadjusted

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intubation during their nursery course, (p<0.0001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005).

Comment [MG10]: Unadjusted

Comment [MG11]: Unadjusted

Strata Results: 24 – 25 weeks Gestation

Comment [AD12]: Do we need to preface some justification for looking within strata?

There were more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, RR=0.74, 95% CI 0.57, 0.98. There was a significantly higher exposure to postnatal steroids for BPD, 20% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

Comment [MG13]: We did not do a test comparing this specific category of race/ethnicity, although we could.

Comment [MG14]: Unadjusted

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 40.6 vs 47.1, p=0.01, and lesser days of mechanical ventilation, 11.3 vs 14.9, p=0.01, and fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

Comment [MG15]: Unadjusted

Comment [MG16]: Unadjusted

Comment [MG17]: Unadjusted

Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[14,14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation.[6] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a non-significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 49% after adjustment for gestational age, center and familial clustering as prespecified, (unadjusted p = 0.046, adjusted p=0.061) We noted however a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD, and significant decreased durations of ventilation, decreased exposure to post natal steroids and a decreased need for intubation in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant without any observed detrimental effects.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 42.2%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

Comment [MG18]: Percent of BPD (by supplemental O2) among our survivors overall

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD

Comment [MG19]: Not significant at p<.05 after adjustment for GA, center, familial clustering

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based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants, and CPAP treatment was associated with significantly decreased durations of ventilation, exposure to post natal steroids and the need for intubation. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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1 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: FW:
Date: Tuesday, October 27, 2009 8:24:38 PM
Attachments: T3 BPD Outcomes - 27OCT09.doc
T1 Patient Description - 27OCT09.doc
T2 Other Outcomes - 27OCT09.doc
SUPPORT CPAP vs Surf Oct 21 09 MG.doc.rtf

Hi Rose
Will you please circulate to all committee members?
Thanks
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 27, 2009 4:59 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Here are the new results for the CPAP-Surf paper. I have made edits to the text to reflect the new numbers (which are almost the same as the old ones).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 27, 2009 7:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Yes Please

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 27, 2009 2:56 PM
To: Gantz, Marie; Finer, Neil
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Marie
Thanks

Neil - shall we get copies for the subcommittee meeting??
Rose
Rosemary D. Higgins, MD

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Program Scientist for the NICHD Neonatal Research Network

From: Gantz, Marie [mgantz@rti.org]
Sent: Tuesday, October 27, 2009 5:05 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE:

Attached is Table 2 for Wally's paper which now includes the ROP/death outcome. FYI, we have the outcome for 93% of SUPPORT infants. You will note that our N is 1316 - we found out this week that for one of our withdrawn patients we needed to exclude all data (like we did for the patient withdrawn from UCSD).

I will send the CPAP-Surfactant tables soon.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 26, 2009 2:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: WCarlo@PEDS.UAB.edu; Das, Abhik
Subject:

Hello Everyone
I am querying you to determine if we will have enough time to redo all the CPAP-Surf Tables and data with the final data before the meeting on Wednesday. I would like to get the committee's input on that manuscript and get it in final shape. I obviously also want to know when we will see the final ROP data set for the SpO2 paper. These questions are key regarding our agenda on Wednesday.
Please let me know where we are?
We are also awaiting the final data etc to finalize the Consent paper.
I would like to get this into submission as soon as we can
I look forward to hearing from you.
Neil

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Table 3. BPD outcomes for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk for CPAP vs Surfactant (95% CI)
Death at any time while hospitalized	16% (109/663)	20% (128/653)	0.84 (0.67, 1.05)
Death by 36 weeks PMA	14% (94/663)	17% (114/653)	0.81 (0.63, 1.03)
BPD (physiologic definition)	39% (223/569)	41% (219/539)	0.99 (0.87, 1.14)
BPD (physiologic definition) or death by 36 weeks PMA	48% (317/663)	51% (333/653)	0.95 (0.85, 1.05)
BPD (supplemental O2)	40% (228/569)	44% (239/539)	0.93 (0.82, 1.06)
BPD (supplemental O2) or death by 36 weeks PMA	49% (322/663)	54% (353/653)	0.91 (0.82, 1)
ROP	14% (70/517)	14% (68/480)	0.95 (0.7, 1.28)
ROP or death	28% (176/620)	32% (193/601)	0.87 (0.74, 1.03)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3: BPD outcomes for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk for CPAP vs. Surfactant (95% CI)
Death at any time while hospitalized	24% (68/285)	32% (90/280)	0.74 (0.57, 0.98)
Death by 36 weeks PMA	20% (57/285)	29% (82/280)	0.68 (0.5, 0.92)
BPD (physiologic definition)	55% (125/228)	55% (108/198)	1.06 (0.91, 1.25)
BPD (physiologic definition) or death by 36 weeks PMA	64% (182/285)	68% (190/280)	0.96 (0.85, 1.07)
BPD (supplemental O2)	54% (122/228)	54% (106/198)	1.05 (0.9, 1.23)
BPD (supplemental O2) or death by 36 weeks PMA	63% (179/285)	67% (188/280)	0.95 (0.84, 1.06)
ROP	23% (47/202)	31% (55/175)	0.75 (0.54, 1.05)
ROP or death	42% (112/266)	55% (144/261)	0.74 (0.62, 0.89)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 3. BPD outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk for CPAP vs. Surfactant (95% CI)
Death at any time while hospitalized	11% (41/378)	10% (38/373)	1.06 (0.7, 1.6)
Death by 36 weeks PMA	10% (37/378)	9% (32/373)	1.12 (0.72, 1.75)
BPD (physiologic definition)	29% (98/341)	33% (111/341)	0.92 (0.74, 1.15)
BPD (physiologic definition) or death by 36 weeks PMA	36% (135/378)	38% (143/373)	0.94 (0.78, 1.13)
BPD (supplemental O2)	31% (106/341)	39% (133/341)	0.83 (0.68, 1.01)
BPD (supplemental O2) or death by 36 weeks PMA	38% (143/378)	44% (165/373)	0.87 (0.73, 1.03)
ROP	7% (23/315)	4% (13/305)	1.86 (0.94, 3.67)
ROP or death	18% (64/354)	14% (49/340)	1.25 (0.88, 1.77)

Relative risks are adjusted for GA stratification, center and familial clustering.
Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

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Table 1. Patient Description for CPAP vs. Surfactant

Variable	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
GA (weeks)	24-25	43% (285/663)	43% (280/653)	0.9686
	26-27	57% (378/663)	57% (373/653)	
Male		52% (342/663)	57% (370/653)	0.0646
Race/ethnicity	Non-Hispanic Black	38% (254/663)	36% (235/653)	0.3681
	Non-Hispanic White	38% (250/663)	42% (271/653)	
	Hispanic	21% (138/663)	19% (121/653)	
	Other/unknown	3% (21/663)	4% (26/653)	
Birth weight (grams)	Mean (n=1316)	834.6 ± 188.2	825.5 ± 198.1	0.3962
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6463
Apgar at 1 minute <3		23% (154/661)	26% (167/653)	0.3370
Apgar at 5 minutes <3		4% (26/663)	5% (32/653)	0.3870
PPV in the DR (SUPP03)		66% (435/662)	93% (606/652)	<0.0001*
CPAP in the DR (SUPP03)		81% (538/663)	22% (146/653)	<0.0001*
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	<0.0001*
DR intubation for resuscitation		33% (215/660)	27% (176/652)	0.0271*
Surfactant in DR (SUPP03)		14% (93/660)	51% (335/652)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		67% (443/660)	99% (646/653)	<0.0001*
Chest compressions in DR (SUPP03)		5% (36/660)	6% (40/653)	0.6026
Epinephrine in DR (SUPP03)		2% (13/660)	4% (27/653)	0.0225*
Antenatal steroids (any)		97% (642/663)	96% (623/652)	0.2248
Antenatal steroids (full course)		74% (486/660)	70% (453/649)	0.1232
Death in the DR (SUPP03/SUPP04)		0% (1/663)	1% (5/653)	0.0978

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (106/280)	0.0495*
	Non-Hispanic White	32% (92/285)	43% (120/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.3 ± 139.5	0.0713
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1149
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (SUPP03)		73% (207/284)	95% (267/280)	<0.0001*
CPAP in the DR (SUPP03)		72% (205/285)	22% (62/280)	<0.0001*
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
DR intubation for resuscitation		48% (137/284)	31% (87/280)	<0.0001*
Surfactant in DR (SUPP03)		21% (60/284)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		77% (220/284)	99% (276/280)	<0.0001*
Chest compressions in DR (SUPP03)		9% (27/285)	8% (23/280)	0.5982
Epinephrine in DR (SUPP03)		4% (10/285)	5% (15/280)	0.2854
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (SUPP03/SUPP04)		0% (1/285)	1% (4/280)	0.1715

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Male		52% (195/378)	56% (208/373)	0.2511
Race/ethnicity	Non-Hispanic Black	35% (132/378)	35% (129/373)	0.8733
	Non-Hispanic White	42% (158/378)	40% (151/373)	
	Hispanic	20% (75/378)	20% (76/373)	
	Other/unknown	3% (13/378)	5% (17/373)	
Birth weight (grams)	Mean (n=751)	922.2 ± 180.5	921.0 ± 181.4	0.9325
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.9676
Apgar at 1 minute <3		18% (66/377)	22% (83/373)	0.1034
Apgar at 5 minutes <3		2% (7/378)	3% (13/373)	0.1645
PPV in the DR (SUPP03)		60% (228/378)	91% (339/372)	<0.0001*
CPAP in the DR (SUPP03)		88% (333/378)	23% (84/373)	<0.0001*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
DR intubation for resuscitation		21% (78/376)	24% (89/372)	0.2964
Surfactant in DR (SUPP03)		9% (33/376)	50% (186/372)	<0.0001*
Surfactant in DR or NICU (SUPP03, SUPP04)		59% (223/376)	99% (370/373)	<0.0001*
Chest compressions in DR (SUPP03)		2% (9/375)	5% (17/373)	0.1072
Epinephrine in DR (SUPP03)		1% (3/375)	3% (12/373)	0.0184*
Antenatal steroids (any)		96% (363/378)	94% (352/373)	0.2865
Antenatal steroids (full course)		70% (262/375)	68% (251/371)	0.5146
Death in the DR (SUPP03/SUPP04)		0% (0/378)	0% (1/373)	0.3138

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Table 2. Other outcomes for CPAP vs. Surfactant

Characteristic	Category	CPAP (N=663)	Surfactant (N=653)	Unadjusted P-value
Death in the first week		6% (40/663)	6% (39/653)	0.9630
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=1075)	100.4 ± 42.9	101.4 ± 41.6	0.7047
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=1079)	97.7 ± 43.4	97.0 ± 41.6	0.7883
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=1098)	55.0 ± 37.8	58.5 ± 37.6	0.1229
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=1098)	20.0 ± 23.9	23.2 ± 26.2	0.0331*
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=1082)	53.6 ± 21.7	55.1 ± 20.3	0.2346
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=1098)	16.1 ± 13.1	15.8 ± 14.7	0.7516
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=1098)	3.5 ± 6.9	3.6 ± 7.1	0.7239
Discharge on oxygen (NG03 or NG05)		22% (122/550)	24% (124/519)	0.5067
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		55% (362/655)	49% (318/652)	0.0188*
Pneumothorax (NG03 or SUPP08)		8% (54/663)	6% (36/653)	0.0586
Any air leak in first 14 days (SUPP08)		7% (45/663)	7% (48/653)	0.6901
Medical or surgical NEC (NG03)		13% (83/654)	10% (63/636)	0.1144
PDA requiring surgery (NG03)		11% (73/653)	11% (68/636)	0.7793
IVH grade 3-4 (NG03)		14% (92/642)	11% (72/628)	0.1279
PVL (NG03 or MRI01)		4% (28/643)	4% (26/629)	0.8450
Death or PVL (NG03 or MRI01)		20% (134/663)	23% (147/653)	0.3086
Postnatal steroids for BPD (NG03)		7% (47/649)	13% (83/631)	0.0005*
Postnatal steroids after DOL 21 (SUPP09)		17% (114/659)	23% (149/652)	0.012*
Intubated in DR (SUPP03)		34% (227/660)	93% (609/652)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		77% (508/661)	100% (649/652)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		83% (551/663)	100% (651/653)	<0.0001*

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Table 2. Other outcomes for CPAP vs. Surfactant
Where GA is 24-25 weeks

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week		9% (25/285)	10% (29/280)	0.5217
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=405)	120.7 ± 47.9	119.2 ± 40.5	0.7394
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=407)	117.6 ± 47.1	116.8 ± 43.3	0.8579
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=421)	76.9 ± 34.3	78.1 ± 33.5	0.7269
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=421)	33.1 ± 27.3	37.5 ± 29.0	0.1138
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=421)	66.5 ± 16.8	67.6 ± 16.2	0.5026
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=421)	18.4 ± 13.8	17.7 ± 16.1	0.5998
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=421)	5.2 ± 8.2	5.5 ± 8.6	0.7016
Discharge on oxygen (NG03 or NG05)		32% (69/214)	31% (59/188)	0.8535
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		34% (97/283)	26% (74/280)	0.0429*
Pneumothorax (NG03 or SUPP08)		10% (29/285)	8% (21/280)	0.2629
Any air leak in first 14 days (SUPP08)		8% (23/285)	10% (27/280)	0.5105
Medical or surgical NEC (NG03)		15% (42/279)	13% (35/268)	0.5026
PDA requiring surgery (NG03)		16% (46/279)	17% (46/268)	0.8325
IVH grade 3-4 (NG03)		20% (54/273)	17% (45/265)	0.4022
PVL (NG03 or MRI01)		6% (17/273)	5% (14/265)	0.6385
Death or PVL (NG03 or MRI01)		29% (83/285)	36% (100/280)	0.0941
Postnatal steroids for BPD (NG03)		13% (36/276)	20% (54/264)	0.0209*
Postnatal steroids after DOL 21 (SUPP09)		28% (78/282)	34% (94/279)	0.1213
Intubated in DR (SUPP03)		51% (145/284)	94% (263/280)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		88% (250/285)	99% (278/280)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		94% (267/285)	100% (279/280)	0.0001*

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Table 2. Other outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks

Characteristic	Category	CPAP (N=378)	Surfactant (N=373)	Unadjusted P-value
Death in the first week		4% (15/378)	3% (10/373)	0.3255
Total LOS any hospital (survivors only) (NG03, NG05)	Mean (n=670)	87.5 ± 33.5	91.3 ± 38.8	0.1699
LOS in NRN hospital (survivors only) (NG03, NG05)	Mean (n=672)	85.0 ± 35.4	85.9 ± 36.2	0.7477
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	Mean (n=677)	40.6 ± 32.6	47.1 ± 35.1	0.0126*
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	Mean (n=677)	11.3 ± 16.3	14.9 ± 20.3	0.0122*
DOL of last supplemental oxygen through 36 weeks PMA (survivors to NG03 status only) (SUPP05, SUPP11)	Mean (n=661)	44.7 ± 20.2	47.7 ± 18.8	0.0555
Days on CPAP (survivors to NG03 status only) (NG07)	Mean (n=677)	14.6 ± 12.5	14.8 ± 13.8	0.8425
Days on nasal SIMV (survivors to NG03 status only) (NG07)	Mean (n=677)	2.3 ± 5.6	2.5 ± 5.8	0.6778
Discharge on oxygen (NG03 or NG05)		16% (53/336)	20% (65/331)	0.1911
Alive and off MV (HFV/CV) at 7 days (NG07 or SUPP05)		71% (265/372)	66% (244/372)	0.0977
Pneumothorax (NG03 or SUPP08)		7% (25/378)	4% (15/373)	0.1137
Any air leak in first 14 days (SUPP08)		6% (22/378)	6% (21/373)	0.9107
Medical or surgical NEC (NG03)		11% (41/375)	8% (28/368)	0.1185
PDA requiring surgery (NG03)		7% (27/374)	6% (22/368)	0.4962
IVH grade 3-4 (NG03)		10% (38/369)	7% (27/363)	0.1738
PVL (NG03 or MRI01)		3% (11/370)	3% (12/364)	0.8013
Death or PVL (NG03 or MRI01)		13% (51/378)	13% (47/373)	0.7169
Postnatal steroids for BPD (NG03)		3% (11/373)	8% (29/367)	0.0029*
Postnatal steroids after DOL 21 (SUPP09)		10% (36/377)	15% (55/373)	0.0293*
Intubated in DR (SUPP03)		22% (82/376)	93% (346/372)	<0.0001*
Intubated in DR or NICU in first 14 days (SUPP03, SUPP04)		69% (258/376)	100% (371/372)	<0.0001*
Any intubation (SUPP03, SUPP04, SUPP05, SUPP05a, SUPP07)		75% (284/378)	100% (372/373)	<0.0001*

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of consenting parents of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP or surfactant; those randomized to CPAP had CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings and infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 13167 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group in the delivery room (all p<0.001), and 67% of the CPAP infants received surfactant ~~at any time during their hospitalization~~in either the delivery room or NICU~~,~~. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 498% in the CPAP group versus 54% in the surfactant group, (~~p< 0.05~~RR 0.91, 95% CI 0.82, 1.00,~~Marie can you please provide the RR and CI~~ when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, ~~p=0.03~~RR 0.74, 95% CI 0.57, 0.98). There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, ~~and the~~or ~~need for~~discharge on oxygen ~~at discharge~~. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.0195) and fewer required post natal steroids for BPD, (p<.00104). All infants in the Surfactant arm were intubated, compared with only 8377% of the CPAP infants requiring intubation during their nursery course, (p<0.001). There were no significant differences between the groups for air leaks including pneumothoraces.

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Comment [AD2]: I would provide the relative risk and 95% CI instead of, or in addition to the p value. Same goes for other CPAP vs surfactant outcome comparisons, both here and in the main text.

Comment [MG3]: Unadjusted

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Comment [MG5]: 77% were intubated in the DR or NICU

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Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so

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for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[46], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

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Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of

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clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age stratum, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

Results:

There were 13167 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. Marie can you correct these – we had one additional child and I do not know which arm that infant was in – the Tables need correcting for the actual number as well – they all total 1316 – and we have 1317 There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not statistically significant.

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In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group; , and 67% of the CPAP infants received surfactant at any time during their hospitalizationin the delivery room or NICU, compared to 99% of those in the surfactant group (all p<0.0001). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, p<0.0001, Table 2.

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The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 498% versus 54%, (p < 0.05RR 0.91, 05% CI 0.82, 1.00, when adjusted for gestational age, center and familial clustering as prespecified Marie we need the RR etc as Abhik has asked for)). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, p=0.27RR 0.93, 95% CI 0.82, 1.06. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (4039% vs 41%, p=0.96RR 0.99, 95% CI 0.87, 1.14), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=0.32RR 0.95, 95% CI 0.85, 1.05).

There were no significant differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at dischargeor

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discharge on oxygen. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.019). There were no significant differences between the groups in air leaks in the first 14 days, ~~air leaks~~pneumothoraces during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, (p<0.0001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0005).

Comment [MG9]: If you want oxygen on the day of discharge, that is different and I can get those numbers for you, but what is in the table is discharge on oxygen.

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Comment [MG11]: Unadjusted

Comment [MG12]: Unadjusted

Strata Results: 24 – 25 weeks Gestation

Comment [AD13]: Do we need to preface some justification for looking within strata?

There were ~~significantly~~ more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality while hospitalized 24% vs 32%, ~~p=0.03~~028RR=0.74, 95% CI 0.57, 0.98. There was a significantly higher exposure to postnatal steroids for BPD, 20~~1~~% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

Comment [MG14]: We did not do a test comparing this specific category of race/ethnicity, although we could.

Comment [MG15]: Unadjusted

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, ~~36.8~~40.6 vs ~~46.5~~47.1, p=<0.01, and lesser days of mechanical ventilation, ~~10.7~~11.3 vs 14.9~~2~~, p=<0.01, and ~~less~~ fewer infants received postnatal steroids for BPD, 3% vs 8%, p<0.01.

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Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[~~14~~14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also

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utilized a very permissive approach for intubation and the initiation of mechanical ventilation. Error! Bookmark not defined.[8] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 498%. We also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Comment [MG19]: Adjusted p-value is 0.0621, Unadjusted is 0.0463

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs ~~38.9~~42.2%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

Comment [MG20]: Percent of BPD (by supplemental O2) among our survivors overall

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and

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conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

Comment [MG21]: Not significant at p<.05 after adjustment for GA, center, familial clustering

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18 Aly, H.; Massaro, A. N.; Patel, K., and ElMohandes, A. A. E. Is it safer to intubate premature infants in the delivery room? Pediatrics. 2005; 115(6):1660-1665

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From: Gantz, Marie
To: Everett-Thomas, Ruth
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09
Date: Tuesday, October 27, 2009 1:38:53 PM

Thank you!

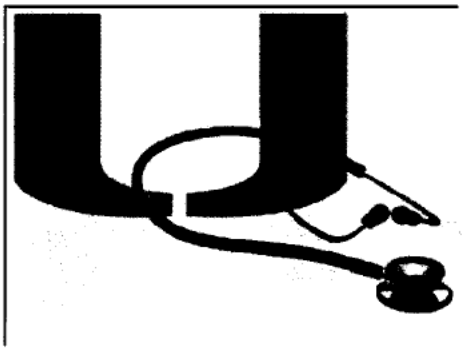
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Everett-Thomas, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, October 27, 2009 1:38 PM
To: Gantz, Marie
Cc: Hobson, Laverne
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Okay, I will make the changes. For the ROP correction on the last exam the infant received in the hospital he met threshold criteria in both eyes and we reviewed his medical records and it was not stated in the hospital chart as threshold being met but according to the MOP he met criteria so we marked yes for threshold for both eyes for the last in hospital exam.

Ruth Everett-Thomas, RN, MSN
Research and Training Specialist
UM-JMH Center For Patient Safety
Institute Building 436 A
Office: 305 585-1465
FAX: 305 585-1475



From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 27, 2009 1:32 PM
To: Everett-Thomas, Ruth
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Thanks, Ruth. Just to clarify, according to the randomization number entered on the SUPP02, it looks like the infant was assigned to blue and that the orange oximeter was placed in error. The reason you received the query is that the treatment assignment entered on the SUPP02 should match what the

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infant was assigned to per the randomization card (blue) rather than what they actually received. Currently, the oximeter assignment entered is orange, not blue. So, that still needs to be changed in the DMS.

What did you edit to resolve the ROP query?

Thanks for all your help!

Marie

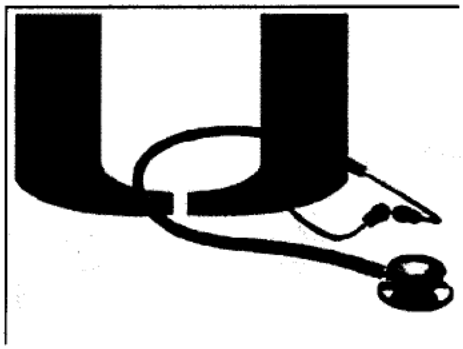
Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Everett-Thomas, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, October 27, 2009 1:20 PM
To: Gantz, Marie
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Yes, we had a protocol violation entered for that baby already in the system because the baby was randomized to orange and was placed initially on a blue Oximeter and when the error was identified we corrected it by putting the infant on the correct monitor and completing a protocol violation. I noticed when we created the protocol violation form the reason was selected as 10 and it should have been 99 (other) and a comment included stating what the violation was.

I corrected this on the protocol violation form by going in an editing the form to select 99.

Ruth Everett-Thomas, RN, MSN
Research and Training Specialist
UM-JMH Center For Patient Safety
Institute Building 436 A
Office: 305 585-1465
FAX: 305 585-1475



From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 27, 2009 12:52 PM
To: Everett-Thomas, Ruth
Cc: Duara, Shahnaz; Hobson, Laverne
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Thanks so much, Ruth. Would you please let me know what changes you made to the ROP data? Also,

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did you resolve the query regarding the randomization of infant (b) (6) If so, please let me know what the result was. I really appreciate your help!

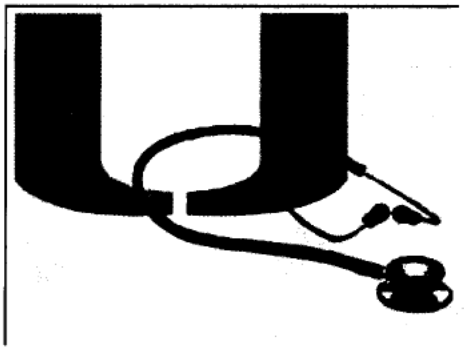
Thanks!
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Everett-Thomas, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, October 27, 2009 12:48 PM
To: Gantz, Marie
Cc: Duara, Shahnaz; Hobson, Laverne
Subject: FW: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Good afternoon Maria, we have corrected the ROP query from our site this morning and after making the corrections we transmitted.

Ruth Everett-Thomas, RN, MSN
Research and Training Specialist
UM-JMH Center For Patient Safety
Institute Building 436 A
Office: 305 585-1465
FAX: 305 585-1475



From: Everett-Thomas, Ruth
Sent: Tuesday, October 27, 2009 12:47 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Good afternoon Maria, we have corrected the ROP query from our site this morning and after making the corrections we transmitted.

Ruth Everett-Thomas, RN, MSN
Research and Training Specialist
UM-JMH Center For Patient Safety

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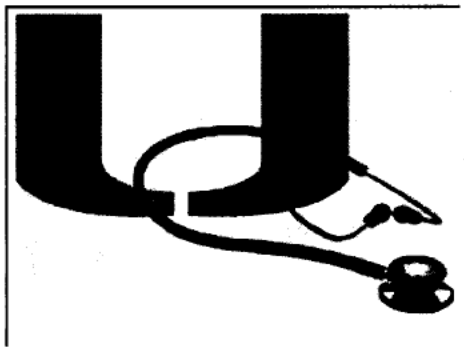
Institute Building 436 A
Office: 305 585-1465
FAX: 305 585-1475



From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 26, 2009 4:35 PM
To: 'Gantz, Marie'; Duara, Shahnaz; Everett-Thomas, Ruth
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Ruth and Shahnaz,
We would like to run the analysis and need the final queries from your site. Please let us know if you will have them today.

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, October 26, 2009 4:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz; Everett-Thomas, Ruth
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Shahnaz and Ruth,

Attached to this email is the query Rose sent to you on Friday as well as one other query involving ROP. Please respond to these as soon as you can, as we are awaiting this information in order to finalize our data for the SUPPORT manuscripts.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 4:51 PM
To: 'Duara, Shahnaz'; Everett-Thomas, Ruth
Cc: Gantz, Marie
Subject: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

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Please respond to the attached queries as soon as possible

Thanks for all the help

Rose

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From: Michael Cotten
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Kimberley A Fisher; Gantz, Marie; Ronald N Goldberg
Subject: RE: Urgent ROP question
Date: Tuesday, October 27, 2009 10:54:03 AM

Hi Marie...I believe the doc who did hte exam (and wrote the cryptic note) is at a conference and unpageable....we'll make a copy of the exam, cut off the identifiers, and send a pdf by email to her to look at to help us adjudicate...

thanks and we'll get it as fast as we can...

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

Michael Cotten/Pediatrics/mc/Duke
10/27/2009 10:11 AM

To: "Gantz, Marie" <mgantz@rti.org>, "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
cc: "Kimberley A Fisher" <kimberley.fisher@duke.edu>, Ronald N Goldberg/Pediatrics/mc/Duke@mc
Subject: RE: Urgent ROP question(Document link: Michael Cotten)

HI Marie and Rose and Ron and Kim

i'm looking at the exam sheet and see where the zone 3, stage 2, plus comes from...and it looks like that's what the ophthalmologist wrote..i have a

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call in to the examining ophthalmologist and will fax her the sheet to see if we've misinterpreted what she's written (or if i have to, i'll walk it across the street)....

i'll let you know as soon as I hear...

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Gantz, Marie"
<mgantz@rti.org>
10/27/2009 09:54 AM

To: "Kimberley A Fisher" <kimberley.fisher@duke.edu>
cc: "Michael Cotten" <cotte010@mc.duke.edu>
Subject: RE: Urgent ROP question

Kim – sorry, I should have said stage 2 ROP below instead of stage 3.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Gantz, Marie
Sent: Tuesday, October 27, 2009 9:52 AM
To: 'Kimberley A Fisher'
Cc: Michael Cotten
Subject: Urgent ROP question

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Kim,

I have a question for you regarding ROP data for one of your infants. For infant (b) (6) on exam dated 5/27/08, both eyes are coded as having vessels in zone III with stage 2 ROP and plus disease. According to Dale Phelps, ROP in zone III is not associated with plus disease, so I'm wondering if either the plus disease or the zone might have been entered in error? The reason for my concern is that if the zone was actually II then the infant met criteria for threshold ROP and would have a negative outcome instead of a positive one. We're trying to finalize the ROP outcome, so if you could check into that for me and let me know as soon as possible what the result is I would really appreciate it. Thank you so much!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Saturday, October 17, 2009 3:27 PM
To: higginsr@mail.nih.gov; Gantz, Marie
Cc: Ronald N Goldberg; Michael Cotten
Subject: Queries

Rose
Here are the latest lists of queries that were sent to Ron and Mike that have been completed. Please let me know if there is anything else that you need.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970 (b) (6)
Email: kimberley.fisher@duke.edu
----- Forwarded by Kimberley A Fisher/Pediatrics/mc/Duke on 10/17/2009 03:24 PM -----

Ronald N
Goldberg/Pediatrics/mc/
Duke

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To
Kimberley A Fisher/Pediatrics/mc/Duke@mc,
10/17/2009 12:30 PM Michael Cotten/Pediatrics/mc/Duke@mc
cc

Subject

"Higgins,
Rosemary
(NIH/NICHD) [E]"
<higginsr@mail.ni To
h.gov> "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>,
"cotte010@mc.duke.edu" <cotte010@mc.duke.edu>,
" (gloria.siaw@duke.edu)" <gloria.siaw@duke.edu>,
10/17/2009 08:19 "kimberly.fisher@duke.edu"
AM <kimberly.fisher@duke.edu>
cc
"mgantz@rti.org" <mgantz@rti.org>
Subject

Hi,
Attached a SUPPORT missing data/queries. Data lock will occur following DMS transmission on Tuesday October 20. Please try to send all of the requested information at this time (or before).

Thanks for all your help!!!

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Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

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From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09
Date: Monday, October 26, 2009 5:10:16 PM

Rose,
Tomorrow morning first thing someone will look through our info.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 26, 2009 4:35 PM
To: 'Gantz, Marie'; Duara, Shahnaz; Everett-Thomas, Ruth
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Ruth and Shahnaz,
We would like to run the analysis and need the final queries from your site. Please let us know if you will have them today.

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, October 26, 2009 4:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz; Everett-Thomas, Ruth
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Shahnaz and Ruth,

Attached to this email is the query Rose sent to you on Friday as well as one other query involving ROP. Please respond to these as soon as you can, as we are awaiting this information in order to finalize our data for the SUPPORT manuscripts.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 4:51 PM
To: 'Duara, Shahnaz'; Everett-Thomas, Ruth
Cc: Gantz, Marie
Subject: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Please respond to the attached queries as soon as possible

Thanks for all the help

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Rose

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz; Everett-Thomas, Ruth
Subject: RE: ****URGENT SUPPORT cross-form queries Center 8 23OCT09
Date: Monday, October 26, 2009 4:33:11 PM
Attachments: URGENT SUPPORT queries Center 8 26OCT09.rtf

Shahnaz and Ruth,

Attached to this email is the query Rose sent to you on Friday as well as one other query involving ROP. Please respond to these as soon as you can, as we are awaiting this information in order to finalize our data for the SUPPORT manuscripts.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 4:51 PM
To: 'Duara, Shahnaz'; Everett-Thomas, Ruth
Cc: Gantz, Marie
Subject: ****URGENT SUPPORT cross-form queries Center 8 23OCT09

Please respond to the attached queries as soon as possible

Thanks for all the help

Rose

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SUPPORT Queries for Center 8-University of Miami

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query resolution Center notes
SUPP02 treatment assignment (CPAP, orange) does not match that on randomization card (CPAP, blue).	

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query resolution Center notes
On SUPP10 exam dated (b) (6) both eyes meet criteria for Threshold ROP per the SUPPORT MOP (vessels in zone III with stage 1 ROP) but Threshold (New Type 1) is not ="Y" on the form.	

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale
Cc: Gantz, Marie
Subject: RE: *****URGENT SUPPORT BPD queries Center 9 23OCT09*******
Date: Monday, October 26, 2009 11:15:38 AM
Attachments: URGENT SUPPORT BPD queries Center 9 23OCT09[1].rtf

---

Rose,
Please, find our queries attached. Sorry about the delay.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 3:22 PM
To: Hale, Ellen; Barbara Stoll; Ellen Hale
Cc: Gantz, Marie
Subject: *****URGENT SUPPORT BPD queries Center 9 23OCT09*******

Hi,
Marie needs clarification on two infants from your site. Can you send this back to us today??
Thanks for all your help!!!!

Rose

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution/ Center notes
On support @36wks per NG07 but off support all day per SUPP11.		Infant on room air and off study monitor. On evening of 1/9 infant back on O2 and monitor not restarted (1/10 36 weeks). Infant weaned to room air 1/12 per PHY01). SUPP11 corrected.

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution/ Center notes
On O2 by NC @36wks per NG07 but on RA by NC with flow<=.5 at all time points on SUPP11. If both forms are correct please F5 on NG07 to verify O2 by NC		Both correct. Infant on and off oxygen during day. On room air at time points.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Michael Cotten
Cc: Das, Abhik; gloria.siaw@duke.edu; Ronald Goldberg; Kimberley A Fisher
Subject: RE: *****URGENT SUPPORT cross-form queries Center 19 23OCT09
Date: Monday, October 26, 2009 10:46:00 AM

Hi all,

As Rose indicates, the NG03 collects information about physical conditions rather than IVH grade to improve consistency across centers. For this reason, we will apply the NRN criteria for the IVH grades to the data entered on NG03 and this will take precedent over the grade of IVH entered on SUPP09. Thanks for your help in clarifying the situation with this infant.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 26, 2009 10:32 AM
To: 'Michael Cotten'; Gantz, Marie
Cc: Das, Abhik; gloria.siaw@duke.edu; Ronald Goldberg; Kimberley A Fisher
Subject: RE: *****URGENT SUPPORT cross-form queries Center 19 23OCT09

Please use definitions from the manual in reporting this one. We ask for descriptors

b. Date of sonogram with most severe findings:	__ __ / __ __ / __ __ __ __ Month Day Year					
c. Blood/echo-density in germinal matrix/sub-ependymal area?	Y	N				
	(1) RIGHT		(2) LEFT			
d. Blood/echo-density in the ventricle?	Y	N			Y	N
e. Ventricular size enlarged with concurrent	Y	N			Y	N

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or prior blood in the ventricles?				
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?	Y	N	Y	N
g. Blood/echo-density in the parenchyma?	Y	N	Y	N

We no longer ask the sites to "grade the IVH" for this very reason!!!
Rose

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Monday, October 26, 2009 10:29 AM
To: Gantz, Marie
Cc: Das, Abhik; gloria.siaw@duke.edu; Ronald Goldberg; Higgins, Rosemary (NIH/NICHD) [E]; Kimberley A Fisher
Subject: RE: *****URGENT SUPPORT cross-form queries Center 19 23OCT09

Hi all...here's the dilemma:

the radiologist called the first head ultrasound result a grade II, but the report mentions ventricular dilatation....but again the summary statement is grade II...I'd call a grade II on both crf's (if it hasn't been alreaady)...the repeat head ultrasound from the next day says: "unchanged mild ventriculomegaly" and continues in the summary calling it a grade II.

the ngo3 asks about dilatation....but here we have a radiologist calling dilatation, classifying a grade II, and then saying 'mild dilatation' the next day.....and the baby ultimately resolved....i think sticking w/ the lower acuity classification, and saying they called dilatation, but it was mild.....would be ok....but will take suggestions from others...

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
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Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Gantz, Marie" <mgantz@rti.org>

10/26/2009 10:06 AM

To "Kimberley A Fisher" <kimberley.fisher@duke.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
cc <cotte010@mc.duke.edu>, <gloria.siaw@duke.edu>, "Ronald

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GOldberg" <goldb008@mc.duke.edu>, "Das, Abhik" <adas@rti.org>
Subject RE: *****URGENT SUPPORT cross-form queries Center 19 23OCT09

Kim,

The reason we are picking this up as a grade III IVH is because the baby is coded on NG03 as having "ventricular size enlarged with concurrent or prior blood in the ventricles" on the left side. When there is both blood in the ventricle and the ventricular size is enlarged, that fits our Network definition for grade III. If there was blood in the ventricle without the ventricular size enlarged we classify that as a grade II. Are the data entered on the NG03 accurate?

Thanks for helping us straighten this out.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Friday, October 23, 2009 5:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu; 'gloria.siaw@duke.edu'; Ronald GOldberg; Gantz, Marie
Subject: Re: *****URGENT SUPPORT cross-form queries Center 19 23OCT09

Rose
It must be in the way we have it coded as this child only has a grade 2. Mike double checked this child from a previous query. I am out of town but will get someone on the phone to resolve this on Monday but here is what we responded to before. The NG03 was incorrectly coded as a grade 3 and I changed the data to reflect Mike's review.

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09. **Resolution: IVH as incorrectly keyed from the NG03 and IVH 2 that is listed on the SUPP09 is correct. Information has been keyed into DMS and sent to RTI.**			**Resolved**

Thanks
Kim

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Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/23/2009 04:48 PM

To Ronald GOldberg <goldb008@mc.duke.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "'gloria.siaw@duke.edu'" <gloria.siaw@duke.edu>

cc "Gantz, Marie" <mgantz@rti.org>

Subject *****URGENT SUPPORT cross-form queries Center 19 23OCT09

Please respond to the attached queries as soon as possible

Thanks for all the help

Rose[attachment "URGENT SUPPORT cross-form queries Center 19 23OCT09.rtf" deleted by Kimberley A Fisher/Pediatrics/mc/Duke]

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Other SUPPORT urgent queries
Date: Monday, October 26, 2009 10:13:20 AM

Those were the only ones, Rose, thanks for sending them. I hope the (b) (6)

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 4:52 PM
To: Gantz, Marie
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Other SUPPORT urgent queries

OK
Sent these – are there any more??
I am going to a (b) (6))!!!!
Let me know and I can send them

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 23, 2009 4:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: Other SUPPORT urgent queries

Rose,

These are the other queries for SUPPORT. Thanks for sending them out.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Frantz, Ivan
Subject: RE: URGENT SUPPORT cross-form queries Center 23 23OCT09
Date: Monday, October 26, 2009 7:32:42 AM

All set

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper #(b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 4:50 PM
To: Frantz, Ivan; Mackinnon, Brenda
Cc: Gantz, Marie
Subject: URGENT SUPPORT cross-form queries Center 23 23OCT09

Please respond to the attached queries as soon as possible

Thanks for all the help

Rose

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From: Vohr, Betty
To: Higgins, Rosemary (NIH/NICHD) [E]; "srhintz@stanford.edu"
Subject: RE: more for extended SUPPORT follow-up
Date: Sunday, October 25, 2009 8:14:40 PM

Susan,
Needs to be done !! Great. I to think that it is necessary to keep all the follow-up PIs invested. It looks like an opportunity for a number of papers from different perspectives.
Just got back from Korea at 6 pm. A little jet lagged. Looking forward to seeing you shortly.
Betty

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Sunday, October 25, 2009 5:06 PM
To: 'srhintz@stanford.edu'; Vohr, Betty
Subject: Re: more for extended SUPPORT follow-up

Extended hypothermia was developed with this same thought - all FU PI's are to be authors

Greta idea!
Rose

----- Original Message -----
From: Susan Hintz <srhintz@stanford.edu>
To: betty vohr <BVohr@WIHRI.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sun Oct 25 13:45:29 2009
Subject: more for extended SUPPORT follow-up

Hi Betty and Rose,

In the SUPPORT neuroimaging and neurodevelopmental outcomes cohort, I think we will have one of the few big cohorts with both 18-22 month Bayley III data and school age quantitative IQ data. This is an opportunity for an examination of predictive capability of the Bayley III, other variables associated with good or poor prediction of school age outcome from 18-22 month data, etc. I think it would be useful to put together a formal secondary analysis proposal for this - I would be happy to work on this with Betty. But, I think we should plan on proposing that ALL the follow-up PI's will be authors on any publication that comes out of it. Having all the follow-up PIs as "real" authors (rather than on a boilerplate) could serve as an incentive for both further participation in analyses and publications, and also to make sure that patients are tracked and get in to be seen at school age.

This would be many co-authors, but I think there is probably a precedent for such?

Thanks -

Susan

--
Susan R. Hintz, M.D., M.S. Epi

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Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
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From: Laptook, Abbot
To: Finer, Neil
Cc: WCarlo@PEDS.UAB.edu; "adas@rti.org"; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: NRN Calls- SUPPORT Call
Date: Friday, October 23, 2009 7:10:12 PM

Neil
Understood and tx for the thoughtful remarks. I would be happy to work with Michelle on a severity of BPD paper. Tx, AL

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, October 23, 2009 6:53 PM
To: Laptook, Abbot
Cc: WCarlo@PEDS.UAB.edu; 'adas@rti.org'; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: RE: NRN Calls- SUPPORT Call

Hi Abbot
I thought your detailed points required some response. You are the only outside person apart from Wally and Abhik that has sent any comments.
I have made changes as per your first suggestions
The manuscript length if we do to NEJM is already at the limit
The issues that you raise however are important
The gender issue is of concern to me but I have been advised by our statistical advisors that as it is not significant and as we did our pre-specified adjustments, that we should not readjust for this.
As for the physiologic definition a large number of children were not challenged and the diagnosis is not at all as clear using this definition, but we committed to report it and will.
I happen to believe that the difference in death in the early gestation strata is the very strongest data to date to support the use of early CPAP – exactly why needs to be further looked into the causes of death do not appear that different and I have always worried about intubation and its negative physiological effects. I know that death was not a pre-specified Primary but it is the most important outcome so I think even the NEJM will not have a problem with us reporting it as we have. The TOBY Trial is a good example of reporting about secondary outcomes. I have tried not to over emphasize but merely state the outcome
We need a separate publication to look at the severity of BPD and longer term outcomes – a repeat of the NRN paper (Ehrenkranz, R. A.; Walsh, M. C.; Vohr, B. R.; Jobe, A. H.; Wright, L. L.; Fanaroff, A. A.; Wrage, L. A., and Poole, K. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec; 116(6):1353-60; ISSN: 1098-4275
The SUPPORT trial will be stronger evidence as it is all from a prospective trial etc. Here we can discuss various levels of severity including the need for CPAP/Vent at 36 weeks. This paper would be a great place to go into detail about the Physiologic definition- Maybe you and Michelle should write this.
I did not want to have the current paper try to cover too much ground and would like to see a quick publication because I think it is important as is the SpO2 paper.
Anyway, I very much appreciate your input.
Be well
Neil

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From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Friday, October 23, 2009 8:17 AM
To: Finer, Neil
Cc: WCarlo@PEDS.UAB.edu; HigginsR@mail.nih.gov
Subject: RE: NRN Calls- SUPPORT Call

Neil
Excellant start to a seminal paper. I have a few comments:
1) I think there should be a clear statement of hypothesis in the abstract and in the introduction; Right now it appears in the Methods.
2) Methods
a. Antenatal consent is buried at the end and may be better placed earlier in the description of how we got this done in the DR.
b. Second paragraph of the description of the surfactant arm it is stated that intubation for either group could be performed at any time for a series of indications. However when the surfactant group has been extubated they are cared for per the standards of the NICU so this may confuse some readers. Could remedy this by amending the last sentence of the preceding paragraph as follows:
"Once extubated surfactant infants were treated using NICU standard of care *including indications for re-intbutaion*."
c. Safety outcomes monitored: do we want to add CPR in the DR?
d. Should you state the guidelines for post-natal steroid use?
3) Results:
a. No signficant differences in sex; seems like a trend toward a difference inspite of randomization
b. Will there be a table for the primary outcome?
c. Should there be a statement regarding extent of compliance with the protocol.
4) Discussion:
a. Should the trend in gender differences be discussed re our outcomes
b. I think you will need to spend more space discussing the issue of differences in BPD when using oxygen use vs the physiologic O2 challenge. Some will look at this as minimizing the extent of differences reported so best to place the two observations in perspective.
c. Differences in deaths for the lower strata: can we categorize the time of death and maybe associated morbidites for the infants that died within each group strata?
d. Will differences in severity of BPD between groups be a subject of another manuscript? Some will have difficulty in putting these observations in their proper place withtout that altougth the death results I would assume would weigh quite heavily with readers.
Hope this helps, Tx, AL

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, October 11, 2009 6:25 PM
To: Wally Carlo, M.D.; Huitema, Carolyn Petrie; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Laptook, Abbot; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject: RE: NRN Calls- SUPPORT Call

Hello Everyone
I thought that this went to all the Subcommittee – Please review the SUPPORT Manuscript for CPAP vs Surf. Your input is essential. Marie will insert the final numbers etc once we have the results of all the queries.
I look forward to your comments and critiques
Many thanks
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, October 07, 2009 8:34 AM

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To: Huitema, Carolyn Petrie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject: RE: NRN Calls- SUPPORT Call

I would like to get comments on the O2 sat paper from the committee members. I have heard from Rose, Neil, Marie and Abhik as we had worked on the previous draft. I would appreciate any comments as soon as possible so I can have with everyone's input by the SC meeting.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Wednesday, October 07, 2009 8:26 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Wally Carlo, M.D.; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject: RE: NRN Calls- SUPPORT Call

Reminder for today's call:

Materials for this call are attached to the email.

The SUPPORT call has been scheduled for

Wednesday, October 7th
SUPPORT 10:30-11:30am ET

For all calls please dial

Within the USA
866-675-(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:
(b) (6)

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Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: *****URGENT SUPPORT BPD queries Center 9 23OCT09*******
Date: Friday, October 23, 2009 5:09:29 PM

Rose,
I will be back in the office on Monday. I will take care of this first thing Monday morning.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 3:22 PM
To: Hale, Ellen; Barbara Stoll; Ellen Hale
Cc: Gantz, Marie
Subject: *****URGENT SUPPORT BPD queries Center 9 23OCT09*******

Hi,
Marie needs clarification on two infants from your site. Can you send this back to us today??
Thanks for all your help!!!!

Rose

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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, October 23, 2009 4:51 PM
To: Duara, Shahnaz; Everett-Thomas, Ruth
Cc: Gantz, Marie
Subject: ****URGENT SUPPORT cross-form queries Center 8 23OCT09
Attachments: URGENT SUPPORT cross-form queries Center 8 23OCT09.rtf

Please respond to the attached queries as soon as possible

Thanks for all the help

Rose

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SUPPORT Cross-Form Queries for Center 8-University of Miami

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution/ Center notes
SUPP02 treatment assignment (CPAP, orange) does not match that on randomization card (CPAP, blue).			

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: Other SUPPORT urgent queries
Date: Friday, October 23, 2009 4:41:59 PM
Attachments: URGENT SUPPORT cross-form queries Center 19 23OCT09.rtf
URGENT SUPPORT cross-form queries Center 23 23OCT09.rtf
URGENT SUPPORT cross-form queries Center 16 23OCT09.rtf
URGENT SUPPORT cross-form queries Center 8 23OCT09.rtf
URGENT SUPPORT cross-form queries Center 11 23OCT09.rtf
URGENT SUPPORT cross-form queries Center 18 23OCT09.rtf

Rose,

These are the other queries for SUPPORT. Thanks for sending them out.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			

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SUPPORT Cross-Form Queries for Center 23-Tufts University

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution Center notes
NG02 birth time (10:45) does not match SUPP03 delivery time (11:45).			

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center's notes
Per SUPP08 infant had IVH grade 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	

F5 noted on the SUPP09; however, blood/echodensity in the parenchyma is recorded on the NG03 and MRI01 which meets definition for IVH grade IV.

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SUPPORT Cross-Form Queries for Center 8-University of Miami

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP02 treatment assignment (CPAP, orange) does not match that on randomization card (CPAP, blue).			

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SUPPORT Cross-Form Queries for Center 11-University of Cincinnati

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution-Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 10 but severe IVH is not recorded on NG03.			

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SUPPORT Cross-Form Queries for Center 18-University of Texas-Houston

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center's notes
SUPP08 AE (3=Severe IVH) entered for DOL 373 (b) (6) Please F5 if date is correct or edit date if not.			

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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: URGENT SUPPORT BPD queries Center 11 23OCT09 (3)
Date: Friday, October 23, 2009 4:10:42 PM

Hi Rose,
This edit should be correct now. Thanks,
Kurt

On 10/23/09 3:21 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
> Marie is missing one item from your site for SUPPORT - can you please send this today???
> Thanks
> Rose

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From: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]; Wilson, Leslie Dawn
Cc: Gantz, Marie
Subject: RE: ******URGENT SUPPORT BPD queries Center 11 23OCT09*****
Date: Friday, October 23, 2009 3:20:23 PM

We are center 12....I think you meant to send this to Cincinnati ☺
Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 23, 2009 3:18 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Gantz, Marie
Subject: ******URGENT SUPPORT BPD queries Center 11 23OCT09*****

Hi,
Marie need clarification on one final infant - can you send this back today??
Thanks for all your help!!
Rose

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From:	Zaterka-Baxter, Kristin
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Gantz, Marie; Das, Abhik
Subject:	FW: Urgent SUPPORT BPD queries
Date:	Friday, October 23, 2009 3:16:29 PM
Attachments:	URGENT SUPPORT BPD queries Center 11 23OCT09.rtf URGENT SUPPORT BPD queries Center 9 23OCT09.rtf
Importance:	High

Hi Rose,

I think you might get a quicker response; would you mind terrible sending these two queries?

Thanks,
Kris

From: Gantz, Marie
Sent: Friday, October 23, 2009 3:09 PM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: Urgent SUPPORT BPD queries

Hi Kris,

Would you mind sending out these two queries today as urgent requests for SUPPORT? These are cases where the BPD query remains unresolved and the conflicting data impacts how the infant will be classified for BPD.

Thanks!
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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SUPPORT BPD Queries for Center 11-University of Cincinnati

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA(b) (6)

Query	Query 2	Query resolution: Center notes
On support @36wks per NG07 but off support all day per SUPP11.	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution Center notes
On support @36wks per NG07 but off support all day per SUPP11.		

Center ID number=9=Emory University Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution Center notes
On O2 by NC @36wks per NG07 but on RA by NC with flow<=.5 at all time points on SUPP11. If both forms are correct please F5 on NG07 to verify O2 by NC		

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From: Zaterka-Baxter, Kristin
To: Gantz, Marie; david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.; Archer, Stephanie (NIH/NICHD) [E]
Subject: REMINDER: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call
Date: Friday, October 23, 2009 8:58:25 AM

Reminder for the call this afternoon at 4:00 PM EST

Call in number: **1-866-675-**(b) (6)
Pass code: (b) (6) (the "#" sign at the end is required)

Thanks,
Kris

From: Gantz, Marie
Sent: Wednesday, October 21, 2009 7:53 PM
To: Zaterka-Baxter, Kristin; 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

Attached are the following documents for the ROP adjudication call.

1) **ROP adjudication data – ROP status unknown 21OCT09.pdf** – This document contains data from ROP exams (form SUPP10) and 18 Month Follow-up (form NF05) for the 97 infants who survived to discharge and are missing the final ROP outcome.
2) **MOP instructions for ROP data.pdf** – This document contains instructions for completing the SUPP10 and vision-related items on NF05 from the SUPPORT and Follow-up Manuals of Operations.
3) Copies of SUPP10 and NF05 for reference.

Please let me know if you have any questions.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Zaterka-Baxter, Kristin
Sent: Wednesday, October 14, 2009 11:38 AM
To: 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

Dear all,

We have scheduled a conference call for **Friday, October 23, 2009 from 4:00 = 5:00PM (EST)** to discuss a process to adjudicate cases with unclear ROP outcome. Contacts below:

Call in number: 1-866-675(b) (6)

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Pass code: (b) (6) (the "#" sign at the end is required)

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, October 12, 2009 2:48 PM
To: 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dear all,

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale; Gantz, Marie; Zaterka-Baxter, Kristin; david.wallace@duke.edu
Cc: Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call
Date: Thursday, October 22, 2009 10:05:03 AM

OK; then we can discuss there how best to use the information Marie supplied, and if you need anything else.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 22, 2009 9:49 AM
To: Das, Abhik; Phelps, Dale; Gantz, Marie; Zaterka-Baxter, Kristin; david.wallace@duke.edu
Cc: Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

This friday is a plannig meeting for the actual adjudication

Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Das, Abhik [adas@rti.org]
Sent: Thursday, October 22, 2009 9:45 AM
To: Phelps, Dale; Gantz, Marie; Zaterka-Baxter, Kristin; david.wallace@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

Dale:

These documents are meant to provide you relevant information that helps adjudicate the ROP status for these babies, so that we can potentially assign a primary outcome to at least some of them. The committee can decide how best to use this information. My thought is that while the adjudication would be a collective process that can only happen at the meeting itself, considering that there are 97 infants to adjudicate and the meeting is only scheduled for an hour, perhaps the committee members can consider coming to some preliminary judgments beforehand. Then the meeting can go over only those cases where there is initial disagreement among the members.

Thanks

Abhik

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 21, 2009 8:50 PM

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To: Gantz, Marie; Zaterka-Baxter, Kristin; david.wallace@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

Please clarify what we should do with these documents. I think we are just to familiarize ourselves with what we have at this point, but not to try and do any judgments for the call.

Is this correct?

Dale

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 21, 2009 4:53 PM
To: Zaterka-Baxter, Kristin; david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call
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Please let me know if you have any questions.

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Marie

Marie Gantz, Ph.D.
Research Statistician
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Sent: Wednesday, October 14, 2009 11:38 AM
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Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

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Call in number: 1-866-675(b) (6)

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Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
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RTP, NC 27709-2194 USA
(tel) 919-485-7750
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Federal Express/UPS/DHL Shipping Address:
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3040 Cornwallis Road
RTP, NC 27709 USA

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From:	Stevens, Timothy
To:	Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"
Cc:	"Richard Ehrenkranz"
Subject:	School Age Breathing Outcomes
Date:	Wednesday, October 21, 2009 9:51:34 PM
Attachments:	Stevens, SUPPORT School Age Breathing Outcomes, 2009-10-06.xls SUPPORT - School Age Breathing Outcomes Proposal 10-21-09.doc School Age Breathing Outcomes - Modified ISAAC 10-21-09.doc

Hi Rose and Neil,

Attached is the School Age Breathing Outcomes Proposal, a secondary to SUPPORT, along with a symptom questionnaire (modified ISAAC questionnaire) and summary of the interest /resource survey that we circulated over the summer. Richard and I feel it is ready for review by the protocol committee. If you agree, can you forward to the protocol committee?

Thanks

Tim

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Neonatal Research Network Steering Committee votes																	
	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	Total
Query: SUPPORT School Age Breathing Outcomes																	
Voted	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	16
Interest/Willingness to participate in the School age Breathing Outcomes Study?																	
Yes	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	15
No											1						1
Houston	We don't have a pulmonologist right now that would be interested in this or have the time for it. We've have recently recruited a new Division Director who would probably be very interested in it, but he's not here yet. I believe he's coming sometime this summer.																
Brown	Hasbro Children's Hospital/Rhode Island Hospital will participate.																
If yes, specify the Pediatric Pulmonologist who will coordinate this study at your center:																	
Wayne	Debbie Toder or Ibrahim Abdulhamid, dtoder@med.wayne.edu; ihamid@med.wayne.edu, 313-745-5541																
Tufts	William Yee, M.D., email: wyee@tuftsmedicalcenter.org, Telephone: 617-636-7917																
Case	Michael W. Konstan, M.D.; michael.konstan@UHhospitals.org; Telephone: (216) 844-8115																
Cinn	Lisa R. Young, MD; Lisa.Young@cchmc.org; Telephone: (513) 636-6771																
Dallas	Olatunji W Williams; olatunji.williams@utsouthwestern.edu; Telephone: 214 456 4630																
UNM	Hengameh H. Raissy, Pharm.D. and Lea Davies, MD; hheidarian-raissy@salud.unm.edu; (505) 272-5484																
Stanford	Carol Conrad, MD; cconrad@stanford.edu; Telephone: 650 723 5191																
Utah	Derek Uchida MD; Derek.Uchida@hsc.utah.edu; Telephone: 801 662-1761																
Alabama	JP Clancy, MD; jpclancy@peds.uab.edu; Telephone: 205-939-9583/205-939-5381																
Iowa	Timothy D. Starner MD; timothy-starner@uiowa.edu; Telephone: (319) 335-7265																
Emory	Michael S. Schechter, MD, MPH; msschec@emory.edu; Telephone: 404 727-0710																
Brown	Karen L. Daigle, MD; Kdaigle@Lifespan.org; Telephone: 401-444-8059																
Yale	Pnina Weiss; pnina.weiss@yale.edu: Telephone: 203-785-2480																
Indiana	Robert Tepper; rtepper@iupui.edu; Telephone: 317 274-9647																
Duke	Duke: Stacey Peterson-Carmichael, MD; slpeters@notes.duke.edu or Stacey.peterson-carmichael@duke.edu; Telephone: 919-668-4760 UNC: Stephanie Davis; sddavis@med.unc.edu; Telephone: 919-966-9850																

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Capacity to perform PFT (patients/mo.)	>50	10-20	20	20	275	10	20	10	20	20		55	nlimite	150	15-20	20-30	
Cinn	In 2008, we had approximately 4800 patient encounters in the PFT lab. These encounters included approximately 3100 spirometry maneuvers and approximately 200 research spirometry maneuvers. The PFT lab supports many research studies annually, and is fully equipped to support further research studies.																
Which reference equation do you use to calculate percent predicted?																	
NHANES		1			1					1			1				4
Polgar		1	1														2
Wang	1			1	1	1		1	1						1		7
Dockery									1						1		2
Crapo		1															1
Knudson							1			1							2
Hankinson				1													1
Wayne	generally Polgar; we have used others when required by muli-center trial																
Tufts	NHANES																
Case	Wang – but flexible (can use whatever equations you would like us to use)																
Cinn	Wang (pediatrics); NHANES III (adult)																
Dallas	NHANES > 8 y.o.; Crapo/Polgar < 8 y.o.																
Stanford	Wang and Dockery																
Utah	Wang and Dockery																
Alabama	NHANES for age 6-7 yrs (we also have the capacity to use Knudson if requested)																
UNM	Crapo/Polgar																
Iowa	Knudson &/or Crapo																
Emory	Wang/Hankinson as recommended by the CF Foundation																
Brown	Wang																
Yale	Knudson																
Indiana	Wang																
Duke and UNC	Eigen: 3-6 yr, Wang: 7yr, NHANES ≥8 years of age																
List the PFTs, patient charge, and the specific equipment available to perform the PFTs:																	
Wayne	Spirometry (94010) $80 Residual Air (94240) $40 MedGraphics 1085D																
Tufts	Spirometry Pre & Post $1091 Professional Interpretation fee $41 Sensormedics Vmax Legacy (Will be changing to the Sensormedics Vmax Encore in future)																

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	Case	Spirometry (all parameters mentioned above) $100 Jaeger Spirometry (bronchodilator response) $150 Jaeger Oxygen saturation $56 Nellcor	
	Cinn	Spirometry (pre/post) see below VMax Spectra (3 systems); VMax Encore (2 systems) Spirometry only $211 Spirometry (pre/post) $352 These charges represent combined technical and professional interpretation charges for clinical studies. Research studies are negotiated as a % of the clinical charge from the research compendium.	
	Dallas	Spirometry with Bronchodilator $ 352.00 Computer – Collins and KoKo Antibacterial/viral filters Albuterol and disposable nebulizer $30.00 Sidestream nebulizer Medication: Albuterol or Xopenex	
	Utah	Spirometry before & after BD $152.46 Collins/Med Graphics MDI Treatment $41.16 Oximetry $58.43	
	Alabama	We have primary and secondary equipment as noted below. The charge covers the oversight/administrative costs of the physician, the time of the RT, disposable equipment costs, cleaning, and maintenance/equipment upkeep. Spirogram (FVC, FEV1, FEF25%-75%) $90 Vmax (Cardinal Health System) Spirogram (FVC, FEV1, FEF25%-75%) Renaissance (Puritan Bennett)	
	UNM	Spirometry (without bronchodilator) $156.00 MedGraphics Spirometry (pre and post bronchodilator administration) $319.00 MedGraphics Methacholine challenge $819.00 MedGraphics	
	Iowa	Pre-Post Spirometry $75.00 Koko nSpire Pulse oximetry $25.00 (if we are doing this)	
	Emory	Spirometry $32* Medgraphics spirometer (several) Pre and post spirometry $76* Medgraphics Plethysmograph Various* Medgraphics Elite Body Box *Negotiable depending on study	
	Brown	Bronchospasm evaluation Technical: $406 Sensormedics Vmax 22 + Professional: $150 + Drug: $3	
	Yale	Spirometry: pre/post bronchodilator (FEV1, FVC, FEV1%, FEF25-75%, PEF) $389.03 Collins cpl #2136 Spacer $9.90 Oximetry $41.37	
	Indiana	Spirometry Research -$175 (bronchodilator response) Sensormedics	
	Duke	Spirometry no bronchodilator $327 Spirometry pre/post $530.00 Cardinal Health/Viasys Koko Spirometer @ Raleigh Consultative Services	

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UNC	Spirometry no bronchodilator $214 Spirometry pre/post $348 Sensormedics Koko Spirometer	

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SUPPORT - School Age Breathing Outcomes Study

A Proposal for the NICHD Neonatal Research Network

October 21, 2009

Timothy P. Stevens, MD, MPH

Richard A. Ehrenkranz, MD

Neil N. Finer, MD

Proposal Date: October 21, 2009

Contact Information:
Timothy P. Stevens, MD
Associate Professor of Pediatrics
Division of Neonatology
Golisano Children's Hospital at Strong
University of Rochester
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone: 585-275-2972
Fax: 585-461-3614
Email: timothy_stevens@urmc.rochester.edu

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Synopsis: For SUPPORT– Breathing Outcomes Study (SUPPORT-BOS) patients, we propose to extend pulmonary follow-up to perform pulmonary function testing at 6-7 years of age. Longer term, longitudinal pulmonary follow up of SUPPORT patients will provide important data on three critical outcomes of the Trial, 1) do the SUPPORT Trial interventions, management with high vs. low oxygen saturation targets and early CPAP vs. prophylactic surfactant and ventilation, result in improved lung function, reduced respiratory symptoms and less need for pulmonary care at 6-7 years of age; 2) do the pulmonary benefits of SUPPORT reduce reaction or susceptibility to secondary pulmonary insults such as lung irritants, infections and allergens during childhood; and 3) are the pulmonary benefits of SUPPORT observed at 18-22 months of age sustained during childhood. The primary outcome will be comparison of the FEV_1 ratio for infants in each of the four SUPPORT treatment groups at 6-7 years of age. Important secondary outcomes will include forced vital capacity (FVC), forced midexpiratory flow rate (FEV_{25-75}), ratio of FEV1 to FVC (FEV%), peak expiratory flow velocity (PEF) and prevalence of symptomatic airway dysfunction and need for medically attended pulmonary care. By evaluating pulmonary function at school age, the SUPPORT – School Age Breathing Outcomes Study will not only provide valuable data on the long term pulmonary effects of SUPPORT but also provide mechanistic insights into the primary and secondary causes of pulmonary morbidity among preterm infants during childhood.

Specific Aims: The SUPPORT-School Age Breathing Outcomes Study will address 3 specific aims.
Specific Aim #1 – Measure the effect of the SUPPORT primary interventions (management with high vs. low oxygen saturation targets and early CPAP vs. prophylactic surfactant and ventilation) on pulmonary function, respiratory symptoms and need for pulmonary care.

Hypothesis #1a - Relative to infants managed with a higher SpO2 range, infants whose neonatal lung disease was managed with a lower targeted SpO2 range will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care and improved pulmonary function (greater FEV_1, FEV_{25-75}, forced vital capacity and peak flow velocities) at 6-7 years of age, regardless of whether they developed BPD or not.

Hypothesis #1b - Relative to infants managed with prophylactic surfactant and conventional ventilation, infants whose neonatal lung disease was managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care and improved pulmonary function at 6-7 years of age, regardless of whether they developed BPD or not.

Specific Aim # 2 – Evaluate the effect of neonatal management with high vs. low oxygen saturation targets on the pulmonary response to secondary pulmonary irritants, such as environmental tobacco smoke exposure, inhaled allergens and respiratory infections during childhood by comparing pulmonary function among infants exposed to secondary respiratory irritants by SUPPORT oxygen saturation target assignment.

Hypothesis #2a (A Novel Second Hit Hypothesis)- Among infants who are exposed to post-neonatal (home or outpatient) environmental respiratory irritants such as tobacco smoke, household allergens or acute viral respiratory illnesses requiring hospitalization, infants whose neonatal lung disease was managed with a lower rather than higher targeted SpO2 will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care and improved pulmonary function at 6-7 years of age, regardless of whether they developed BPD or not.

Hypothesis #2b (A Novel Second Hit Hypothesis)- Among infants who are exposed to post-neonatal (home or outpatient) environmental respiratory irritants such as tobacco smoke, household allergens or acute viral respiratory illnesses requiring hospitalization, whose neonatal lung disease was managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care and improved pulmonary function at 6-7 years of age, regardless of whether they developed BPD or not.

Specific Aim #3 – Evaluate the relationship between symptomatic airway dysfunction at 18-22 months of age measured by parental report as part of the Breathing Outcomes Study and respiratory symptoms, need for pulmonary care and pulmonary function at 6-7 years of age. By following individual infants from birth, through 18-22 months and on to 6-7 years of age, this aim will evaluate how pulmonary morbidity, the

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pulmonary benefits of SUPPORT and the burden of pulmonary care for extremely premature infants evolves over time. This information will be valuable in developing recommendations for pulmonary follow up and care and estimating treatment costs of future extremely preterm infants.

> Hypothesis #3 – BPD and symptomatic airway dysfunction at 18-22 months of age (primary outcome of the Breathing Outcomes Study) better predict respiratory symptoms and need for pulmonary care than abnormal pulmonary function at 6-7 years of age.

Background:

Extremely premature infants are born during a critical juncture in lung development. Perinatal environmental exposures or insults occurring during this time, such as supplemental oxygen and mechanical ventilation, interfere with normal pulmonary development resulting in impaired lung growth, structure and function. Although infants who develop BPD are at greatest risk, respiratory symptoms and need for pulmonary treatment are a significant morbidity for many preterm children. Longitudinal studies in term infants suggest that the origins of wheezing and asthma may begin in early life when genetically susceptible or environmentally sensitized infants are exposed to specific allergens, infectious agents or environmental pollutants (1;2). Premature infants, especially very low birth weight infants (VLBW, <1500 grams, approximately 32 weeks' gestation or less), commonly have respiratory exposures to concentrated oxygen and mechanical ventilation, exposures that are associated with high risk for asthma-like episodes of wheezing. How these neonatal respiratory exposures interact with common allergens, infectious agents or environmental pollutants to cause later pulmonary morbidity for premature infants is not known. Greater understanding of the interaction between neonatal and post-neonatal factors may lead to development of improved methods to avoid secondary lung injury among formerly extremely premature infants and to promote their long-term respiratory health. The potential costs are great. Because mean per capita asthma related costs may be 5 times greater for VLBW than normal weight infants, VLBW infants contribute substantially to the public health burden of wheezing in the United States (3;4).

Absence of Long Term Pulmonary Outcome Studies of Randomized Neonatal Oxygen Exposure

There are no longitudinal pulmonary follow up studies of randomized neonatal oxygen or mechanical ventilation exposure on school age pulmonary outcome. The duration of supplemental oxygen in the neonatal period is an important predictor of pulmonary morbidity. Kennedy et al found that 20 days of oxygen had little effect on FEV1, but each additional week of supplemental oxygen after that time was associated with a progressive reduction in FEV_1 of 3% (5). However, duration of oxygen therapy does not discriminate between oxygen as a cause of lung injury and oxygen as a marker for the severity of lung injury. Whether the level of oxygen exposure in the early neonatal period affects the need for later oxygen to treat lung injury cannot be ascertained from current literature. By randomizing oxygen saturation targets and thereby level of oxygen exposure in the early neonatal period, SUPPORT is the only study with the potential to discriminate between the effect of level of concentrated oxygen as a neonatal lung toxicant and duration of supplemental oxygen as a treatment for chronic lung disease. The SUPPORT – School Age Breathing Outcomes study will provide essential information on how the level of oxygen exposure in the neonatal period affects pulmonary function.

Lack of Longitudinal Pulmonary Outcome Studies for Extremely Premature Infants

Cross sectional pulmonary outcome studies have shown that premature infants have impaired pulmonary function through childhood and into young adulthood (5-11). However, less is known about changes in pulmonary symptoms and lung function in individual patients over time. Available longitudinal pulmonary outcome studies have mostly targeted VLBW infants, a population at less risk for BPD than ELBW infants and therefore likely at less risk for ongoing pulmonary morbidity during childhood (12-14). The SUPPORT – School Age Breathing Outcomes Study will provide important longitudinal data on the natural history of pulmonary morbidity among extremely premature infants and will allow the burden of providing pulmonary care for this population to be quantified.

Neonatal Oxidant Lung Injury May Increase Susceptibility to Later, "Second Hit" Pulmonary Injury

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For term infants, post-neonatal environmental exposures such as environmental tobacco smoke, household allergens and lung infections exert long-term effects on lung function. For extremely preterm infants, hyperoxia- and mechanical ventilation-associated lung injury exert long-term effects on lung structure and function, potentially adversely affecting aging and respiratory health into adulthood. Little is known about the interplay between early neonatal respiratory exposures, such supplemental oxygen and mechanical ventilation, and later, post-neonatal environmental exposures on respiratory symptoms and lung function during childhood. Data emerging from animal and human studies suggest that neonatal exposure to concentrated oxygen not only causes direct lung injury but also alters how the lung responds to subsequent respiratory exposures such as inhaled lung irritants, allergens and infectious agents that commonly occur during childhood.

Oxygen Exposure Causes Increased Susceptibility to Respiratory Allergens

Studies in mice, rats, guinea pigs and rhesus monkeys suggest that exposure of the term or preterm lung to oxidant stress for relatively brief periods in the neonatal period is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and reactivity to subsequent environmental challenges (15-19). Schlegle exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in reduced airway number, hyperplasia of bronchial epithelium, increased mucous cells, alterations in airway smooth muscle, airway hyperreactivity, interrupted postnatal basement membrane zone differentiation and reorganization of the airway vascular and immune system. Using supplemental oxygen rather than the stronger oxidant, ozone, Schulman found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyper-reactivity at 2 and 9 days after cessation of oxygen. These studies show that exposure of infants to oxidant lung stress during early postnatal lung development sensitizes the lung, favoring increased airway reactivity, greater mucus production and development of intermittent airway obstruction associated with wheeze (20). By evaluating infants exposed to different levels of oxygen in the neonatal period and analyzing their pulmonary function by exposure to later environmental allergens or irritants (wood or tobacco smoke), the SUPPORT – School Age Breathing Outcomes Study may provide important mechanistic insights into the effects of early neonatal oxygen exposure and later reaction environmental allergens.

Neonatal Oxygen Exposure Causes Increased Susceptibility to Later Acute Respiratory Infections

Epidemiologic studies indicate children who have been exposed to concentrated oxygen in the neonatal period for treatment of RDS and/or BPD are more likely to have viral infections and out-of-school sick days than children who were not exposed to oxygen (21-23). Whereas it is well known that hyperoxia permanently disrupts postnatal lung development, less is known about how neonatal hyperoxia affects the lung's response to later exposure to respiratory pathogens and inhaled toxicants. Recently, in an animal model of hyperoxic lung injury, O'Reilly et al. showed that short-term hyperoxia at levels that are not associated with chronic alveolar changes during postnatal lung development significantly increases the sensitivity of adult mice to acute respiratory infection (24). Unlike infected siblings that developed disease and recovered, oxygen-exposed and infected mice showed enhanced recruitment of inflammatory cells into the lung leading to greater alveolar fibrosis and mortality. In unpublished data, neonatal hyperoxia resulted in significant delay in clearing influenza virus, a finding that may also contribute to greater mortality. These studies imply that neonatal hyperoxia disturbs innate immunoregulatory pathways in lung, which may contribute to the increased susceptibility to respiratory viral infections, greater disease severity and possibly reductions in lung function. By evaluating infants exposed to different levels of oxygen in the neonatal period and analyzing their pulmonary function by number of acute respiratory infections requiring hospitalization during the preschool years, the SUPPORT – School Age Breathing Outcomes Study may provide important mechanistic insights into the effects of early oxygen exposure and susceptibility to acute respiratory infections.

Alveolar Simplification Associated with BPD May Predispose Toward Earlier Lung Aging

BPD has changed over time. Whereas "old" BPD was associated with fibrosis, cystic alveolar changes and airway inflammation, "new" BPD is characterized by less airway involvement but significant alveolar simplification. Because normal lungs in healthy adults undergo emphysematous changes during aging,

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there is concern that premature infants who have suffered alveolar simplification as a result of BPD or extremely preterm birth will have earlier or more rapidly progressive emphysematous changes as they age. A recent study of pulmonary function among young adults (mean age 19 years) who had moderate to severe BPD as preterm neonates found that over 80% showed signs of premature emphysematous changes (25). Hyperoxia may be a cause of alveolar simplification, in part by reducing cell proliferation and airway branching. O'Reilly has shown in laboratory animals that hyperoxia induces p-21, an inhibitor of cell proliferation that has the potential to inhibit alvelolar and airway growth (26;27). Whether management of babies with lower rather than higher saturation targets reduces oxygen exposure to the lung and thereby promotes normal lung growth prevents alveolar simplification has not been studied. The SUPPORT – Breathing Outcomes school age PFT study would measure vital capacity provide inference about lung growth and alveolarization.

Excess Respiratory Symptoms Persist Beyond Pulmonary Function Abnormalities in Preterm Infants
Preterm infants, especially those who develop BPD, are at greatest risk for persistent respiratory symptoms, need for pulmonary care and abnormal pulmonary function during childhood (12;14;23;28). In cohort studies, the prevalence of respiratory symptoms and need for pulmonary care often exceeds the prevalence of objective measurements of abnormal pulmonary function (11;14;29). In a recent study of former preterm compared with healthy term infants assessed as young adults (21 years of age), subjects born preterm had significantly more respiratory symptoms yet no difference in pulmonary function measurements of airway obstruction or reactivity (30). The SUPPORT-School Age Breathing Outcomes Study will measure both prevalence of respiratory symptoms and need for care and objective measures of pulmonary function. We hypothesize that BPD and respiratory symptoms at 18-22 months of age will be more closely predictive of ongoing respiratory symptoms and need at 6-7 years of age than of abnormal pulmonary function.

NIH Recognizes Need for Further Study of Developmental Origins of Altered Lung Physiology
In May 2008, NHLBI issued a request for applications (RFA Number: RFA-HL-08-009), entitled "Developmental Origins of Altered Lung Physiology and Immune Function". The RFA, funded through a R01 mechanism, calls for applications "that propose to perform research that will enhance the understanding of how the pre- and postnatal environments affect the interplay of the lung and immune system during development resulting in sustained changes in lung physiology and immune function that compromise respiratory health and outcomes." Although not responsive to the RO1 due to the lack of associated animal studies, the SUPPORT–School Age Breathing Outcomes Study provides a unique opportunity to study the effect of management with randomized ventilation and oxygen saturation targets on later "second hit" environmental and infectious lung injury and repair.

Summary
The SUPPORT – School Age Breathing Outcomes Study represents a unique opportunity to study the causes of short and long term pulmonary morbidity of preterm infants for several reasons, including:

- Longitudinal follow-up studies of randomized, experimental oxygen and mechanical ventilation exposure are not available and, if not performed by the NICHD Neonatal Research Network, unlikely to be performed in the future.
- By following infants exposed to randomized, experimental exposure to concentrated oxygen and mechanical ventilation through childhood, a "natural experiment" is created in which the effects of early neonatal respiratory exposures on the sensitivity or reaction to subsequent environmental exposures can be studied. Insights gained from this study may provide new insights into the mechanisms causing pulmonary morbidity among preterm infants and to create future opportunities to prevent or treat chronic respiratory disease in these infants.
- Because of its longitudinal design, valuable information will be gained on the natural history of pulmonary morbidity in preterm infants during childhood and allow the burden of treating preterm infants with respiratory to be quantified.

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Methods: The methods described below describe the study population, field work necessary to track potentially eligible patients to school age and gain consent for participation. The methods also describe the tools used to measure the primary and main secondary pulmonary outcomes and collect environmental respiratory exposures that might modify those outcomes.

Study Population:

Inclusion

- Infants enrolled in SUPPORT and Breathing Outcomes Secondary Study
- Capable of performing spirometry
- Consent to participate in School Age Breathing Outcomes

Exclusion

- Failure to participate in School Age Breathing Outcomes

Field Work:

Tracking patients: Tracking will be essential to ensure the best possible follow-up. The tracking program and tracking tool will be similar to those used in the Neuroimagaing Secondary Study (Appendix 1).

Between 18-22 months and 6-7 years of age, two contacts per year will be attempted, one phone call and one yearly mailing with a birthday card and information about respiratory health of preterm infants. Regular contact will aid in keeping contact information of study patients up to date. Two contacts (1 phone and 1 mail contact) per year over 5 years, 10 total, at $35/contact is a total budgeted cost of $350/patient. Although difficult to estimate, it is very likely that the tracking costs of School Age Breathing Outcomes will be substantially reduced by overlap with tracking procedures and effort performed as part of the neuroimaging secondary study.

Consent:

Consent to contact families for possible 6-7 year follow-up will be sought at the 18-22 month visit. Tracking will then commence as noted above. For patients beyond 18-22 months of age when the School Age Breathing Outcomes Protocol is implemented, formal signed consent will be obtained at the time of the 6-7 year follow-up visit. It is expected that the consent process will take ~1/2 hour.

Patient incentive to participate: To facilitate recruitment and retention, a $100 honorarium will be offered to each patient choosing to participate in the SUPPORT – School Age Breathing Outcomes Study.

Outcomes:

Primary Outcome:

- Ratio of forced expiratory volume in 1s (FEV_1) divided by that predicted based on the patients weight, height and sex

Secondary Outcomes:

- Forced vital capacity (FVC)
- Forced midexpiratory flow rate (FEV_{25-75})
- Ratio of FEV_1 to FVC (FEV%)
- Peak expiratory flow velocity (PEF)
- Resting respiratory rate and oxygen saturation
- Prevalence of symptomatic airway dysfunction measured using a symptom questionnaire
- Use of respiratory medications in the preceding 12 months
- Need for medically attended outpatient pulmonary care (ED or office) in the preceding 12 months
- Need for respiratory related hospitalization in the preceding 12 months
- Assessment of correlation between FEV_1 and respiratory symptoms at 6-7 years of age
- Among infants with family history of asthma, to compare symptomatic airway dysfunction, need for outpatient pulmonary care and pulmonary function at 6-7 years of age by SUPPORT intervention.
- Association between respiratory symptoms and measured PFT abnormalities at 6-7 years of age.

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Pulmonary Function Testing:
In 2007, The American Thoracic Society and European Respiratory Society issued a statement confirming that technically acceptable spirometry is possible in preschool aged children and provided guidelines on the performance and reliability of pulmonary function testing in this age group. *Pulmonary function testing for the SUPPORT – School Age Breathing Outcomes Study will be performed in accordance with the ATS / ERS statement (31).*

Spirometry is commonly performed in adults and in school age children (those aged 6–16 yr), but recent reports have confirmed that preschool children are also able to perform these maneuvers (32-38). To optimize the accuracy, reproducibility and comparability of spirometry data across centers, the SUPPORT – School Age Breathing Outcomes Study will adhere to the following ATS / ERS recommendations (31):

1. The flow–volume curve ideally should be presented to the operator in real time with the ability to also view the volume–time trace.
2. The following indices from each spirometry attempt should be available to the operator before the next attempt: FVC, FEV in *t* seconds (FEV*t*), back-extrapolated volume (VBE), and the point at which flow ceases, presented as a proportion of peak expiratory flow (PEF).
3. If it is the subject's first attempt at spirometry, a period of training is essential. The child should be familiarized with the equipment and technician.
4. Interactive computerized incentives (software used to motivate the patient) will be used to encourage the maneuver. The incentive to be used will be a volume-driven incentive or a flow- and volume-driven incentive during the time the maneuvers are to be recorded.
5. Posture and noseclip use will be recorded and reported.
6. The operator should observe the child closely to ensure there is no leak, and that the maneuver is performed optimally.
7. A minimum of three maneuvers will be recorded, but no maximum number is stipulated.
8. Both volume–time and flow–volume curves should be visually inspected. The attempt should be excluded if the flow–volume curve does not demonstrate a rapid rise to peak flow, and a smooth descending limb, without evidence of cough or glottic closure.
9. If the VBE is greater than 80 ml, or 12.5% of FVC, then the curve should be reinspected, but need not necessarily be excluded.
10. If cessation of flow occurs at greater than 10% of peak flow, then this maneuver should be classified as showing premature termination. It may be possible to report timed expiratory volumes from such a maneuver, but FVC and forced expiratory flows should not be reported.
11. The highest FEV*t* and FVC should be reported, after examining data from all of the usable curves, even if they do not come from the same curve.
12. The starting point for FEV*t* should be determined by back extrapolation.
13. The method of identifying best flows should be recorded and reported. If flows are to be reported from the "best" maneuver, then this should be identified as that with the highest sum of FEV0.5 and FVC.
14. Ideally, the subject should produce at least two acceptable curves, where the second highest FVC and FEV*t* are within 0.1 L or 10% of the highest value, whichever is greater. If a single satisfactory maneuver is recorded, then these results should not be excluded simply because of poor repeatability. The number of technically satisfactory maneuvers and the repeatability results should always be reported.

Respiratory Symptom and Healthcare Utilization Questionnaire: Literature suggests that pulmonary morbidity as measured by both respiratory symptoms and pulmonary function testing persists through school age. A recent study suggests that a tendency toward greater frequency and severity of respiratory symptoms may persist beyond the age at which objective pulmonary function tests have normalized.

The respiratory symptom and healthcare utilization questionnaire to be used in this study will be a modified version of the International Study of Asthma and Allergies in Childhood (ISAAC) Questionnaire (separate file). This questionnaire has been well validated in multiple asthma related studies and used in the school age

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follow-up studies of respiratory outcome of preterm infants. (12;39-42). The ISAAC questionnaire is very strong in screening for and quantifying the severity of respiratory symptoms and collecting information on respiratory exposures, triggers and the effects of respiratory symptoms on quality of life. Modifications to the ISAAC Questionnaire that will be introduced by the School Age Breathing Outcomes Investigators are addition of several questions asked previously as part of the Breathing Outcomes Study to obtain health care utilization and respiratory medication histories. From these questions, data on the following respiratory exposures will be obtained:

Primary Exposures:
Environmental Tobacco Smoke (ETS): Presence or absence of ETS exposure will be ascertained using questions shown by Dr. Wakefield and colleagues to correlate with cotinine levels (43;44). These questions were administered as part of the Breathing Outcomes Study at 18-22 months of age and will be administered again at 6-7 years of age.

Environmental Allergens: The number of inhaled environmental allergens to which a child was exposed will be ascertained using the ISAAC-based School Age Breathing Outcomes Questionnaire.

Acute Respiratory Infections: Number of acute respiratory infections receiving medical attention by 18-22 months of age will be ascertained using the Breathing Outcomes 18-22 month Questionnaire, questions # 6a, 7a or 8a of the Breathing. Additional history of the number of number of respiratory infections in the preceding 12 months will be obtained at 6-7 years of age.

Sample Size:
The Newborn Lung Project, a cohort study of VLBW infants at school age served as the basis for the assumptions used to calculate sample size. The Newborn Lung Project, a cohort study of 265 VLBW infants, studied FEV1 ratio (ratio of observed FEV1 divided by that predicted based on the patients weight, height and sex) at school age in patients with and without BPD (n - 59, FEV1 ratio - 0.78, sd - 0.13 and n - 206, FEV1 ratio - 0.88 and sd - 0.14, respectively) (14). Based on these assumptions, an effect size table was calculated (Appendix 2). In the base case (highlighted box in Appendix 2), 120 patients (60 in each SUPPORT treatment group) will be sufficient to detect an 8% difference in FEV1 with 90% power and two-sided alpha of 0.05. An 8% absolute difference in FEV1 ratio was assumed in the base case because it is both clinically significant and a conservative estimate of the expected differences between groups.

Number of Available Patients
Primary Outcome:
Based on enrollment to date, at least 750 patients will be enrolled into the SUPPORT – Breathing Outcomes Study at completion of the study. Assuming a 10% loss to follow up at 18-22 months (estimates based on current enrollment and follow up data), 25% loss to follow up at 6-7 years of age and 25% of potentially eligible patients being unable to perform testing, 384 patients are expected to be available to study (Appendix 3). Based on the 2x2 randomized design of SUPPORT, an estimated 96 patients per study intervention group (Figure 1, cells I-IV) and 192 patients per primary intervention comparison (e.g. - Figure 1, cells I & III vs. cells II & IV) will be available for study.

Fig. 1 NICHD SUPPORT Trial Design, 2 x 2 factorial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment Early CPAP	I Early CPAP + Low SpO2 (96 patients)	II Early CPAP + High SpO2 (96 patients)
Control Prophylactic/Early Surfactant	III Control + Low SpO2 (96 patients)	IV Control + High SpO2 (96 patients)

Hence, the available sample of 192 patients per primary intervention comparison (e.g. - Figure 1, cells I & III vs. cells II & IV) will be more than adequate to detect an 8% differences in FEV1 ratio through a wide range of assumptions of treatment effect (detectable difference) and standard deviation of the data (Appendix 2).

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Analysis by each of 4 treatment groups: With an estimated 96 available patients per each of the 4 treatment groups defined in Figure 1, a sample size of 120 patients will be adequate to detect an 8% difference in FEV1 between each primary treatment group and allow analysis of potential synergy between combinations of treatment modalities.

Secondary Outcomes:

Subgroups of patients with or without BPD: The available study population will be adequate to allow analysis of treatment effect in important subpopulations, including comparison of the SUPPORT intervention effect among infants with and without BPD. Assuming a 35% rate of BPD among study patients, 136 infants (34 per treatment cell, Figure 2, cells I-IV) would be expected to have BPD and 248 infants would not. Again a total of 120 patients would be necessary to detect an 8% difference in FEV1 between SUPPORT Study interventions assuming 90% power, alpha of 0.05, and standard deviation of 12%. Based on these assumptions, the available sample of 136 patients per primary intervention comparison (e.g. - Figure 2, cells I & III vs. cells II & IV) will be more than adequate to clinically significant differences through a wide range of assumptions of treatment effect (detectable difference) and standard variation of the data (Appendix 2).

Fig. 2 - Available Subgroup of Patients with BPD

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment Early CPAP	I Early CPAP + Low SpO2 (34 patients)	II Early CPAP + High SpO2 (34 patients)
Control Prophylactic/Early Surfactant	III Control + Low SpO2 (34 patients)	IV Control + High SpO2 (34 patients)

Analysis by Environmental Tobacco Smoke (ETS) Exposure: Based on assumptions above and assuming 30% of study patients will have environmental tobacco smoke (ETS) exposure, a total of 116 patients (58 per cell I & II in Figure 3) will have ETS exposure. Based on data from former VLBW infants with ETS exposure (4), a larger detectable difference between primary study intervention (high vs. low targeted saturation) is expected. The available study population will be adequate to detect 8% difference in FEV1 between high and low targeted oxygen saturation group among patients with or without ETS exposure with 80% power or a 10% difference between groups with 90% power (Appendix 2 – Sample Size Table). Evaluating the effects of ETS exposure will provide important information on whether the pulmonary benefits of SUPPORT confer resistance to secondary pulmonary irritants such as ETS exposure. Similar analyses will be performed for subgroups of infants with history of acute respiratory infections and inhaled allergen exposure during childhood.

Fig. 3 Available Subgroup of Patients exposed to ETS

	Low SpO2 85% to 89% 192 patients	High SpO2 91 to 95% 192 patients
Environmental Tobacco Smoke Exposure	I 58 Patients	II 58 Patients
No Environmental Tobacco Smoke Exposure	III 144 patients	IV 144 Patients

Analysis Plan

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample ttest, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina). Data will be presented as shown in Appendix 4. Pulmonary function tests will be reported as z-scores, in accordance with the ATS / ERS recommendations for reporting PFT results in preschool and school age children.

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Budget:

In Appendix 3, a total budget of $396,400 is estimated. The budget allows for start up costs of $1,000 per center for IRB and consent preparation, $2500 for equipment and capitated costs for patient tracking and follow up ($350 per patient), spirometry ($350 per patient), administration of the Respiratory Symptom and Healthcare Utilization Questionnaire ($50 per patient) and a participant honorarium ($100 per patient).

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Appendix 1. – Tracking Questionnaire

NICU Network	**SUPPORT School Age Breathing Outcome Secondary 6-7 Year Tracking Form (SEF 01)**

Center: __ Site No: __ Network No: __ __ __ __ Birth Order: __ Mother's Initials: __ __ __, __ __ Follow-up No.: __ __ __ __

This form should be completed for all children enrolled in the SUPPORT Breathing Outcomes secondary study who were alive at the 18-22 month follow up visit.

A. STATUS INFORMATION

1. Were you able to contact the family? Y N

1a . IF YES: (enter all codes that apply from below) ___ ___ ___ ___ ___

1=Saw the family in person
2=Spoke on the phone
3=Emailed and received a reply
4=Sent letter/postcard and have received a reply via mail
5=Other_____

1a1. Date of contact __ __/__ __/__ __ __ __
Month Day Year

1b . IF NO: (enter all codes that apply from below) ___ ___ ___ ___ ___

1=Left voicemail(s) at number that was definitely still the family's and have not heard back
2=Left generic voicemail(s) at number that might not be the family's and have not heard back
3=Sent mail to last known address and have not received response
4=Sent mail to last known address and it was returned
5=Other_____

2. 3-4 year outcome: (enter one code from below) ___

1=Family is planning on attending the 6-7 year visit
2=Family declines further contact
3=The child is deceased
4=All contact currently lost, continuing to look
5=Other_____

B. FORM COMPLETION

1. Date form completed: __ __/__ __/__ __ __ __
Month Day Year

2. Initials of person completing this form: ___ ___ __

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Appendix 2 – Estimates of Available Study Population and Necessary Sample Size

Available Patients

Estimated Available Study Population	**n**	**Remaining N**
Total Enrolled Breathing Outcomes Patients (# anticip	750	750
Loss to follow up at 18-22 months of age (10%)	75	675
Loss to follow up at 6-7 years of age (25%)	166	509
Unable to perform (25%)	125	384
Total Available Study Subjects		**384**

Available Subjects for Subroup Analysis	**Patients (N=384) With BPD (n)**	**Without BPD (n)**
35% Incidence of BPD	136	248
45% Incidence of BPD	173	211

Sample Size Table

	Detectable Difference (Absolute Value)	**High Sat Group**	**Low Sat Group**	**Sample Size (total for 2 groups) 90% Power**	**80% Power**
Primary Outcome					
Calculation using range of mean difference assumptions					
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.13)	214	160
FEV1, mean (sd)	0.08	0.80 (0.14)	0.88 (0.13)	120	90
FEV1, mean (sd)	0.10	0.78 (0.14)	0.88 (0.13)	78	58
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.10	0.78 (0.14)	0.88 (0.14)	84	62
FEV1, mean (sd)	0.10	0.78 (0.16)	0.88 (0.16)	108	82
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.08	0.80 (0.14)	0.88 (0.14)	130	98
FEV1, mean (sd)	0.08	0.80 (0.16)	0.88 (0.16)	170	126
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.14)	230	172
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.14)	300	224

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Appendix 3 - Budget

SUPPORT - School Age Breathing Outcomes Study

Proposed Budget

Start up costs	**Unit Cost**	**Total (20 Centers)**
IRB	$1,000	$20,000
Spirometry Equipment (Cardinal Health Microloop)	$2,500	$50,000
Sub-total Start up Costs		**$70,000**
Capitated Costs	**Per Capita**	**Total (n=384)**
Tracking and Follow up Between 18-22 months and 6-7 years 2 contacts / yr for 5 years (1 mail and one phone contact) @ $35/contact - 10 total	$350	$134,400
Spirometry Testing (pre - post bronchodilator)	$350	$134,400
Questionnaire	$50	$19,200
Participant Honorarium	$100	$38,400
Sub-total Capitation Costs		**$326,400**
Data Center Costs		**TBD**
Grand Total		**$396,400**

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Appendix 4 – Analysis

Outcome	Early CPAP / Low SpO2 Target	Early CPAP / High SpO2 Target	p-value	Control / Low SpO2 Target	Control / High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
Respiratory Symptoms			RR 95% CI			RR 95% CI
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

Outcome	BPD Low SpO2 Target	BPD High SpO2 Target	p-value	Without BPD Low SpO2 Target	Without BPD High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
Respiratory Symptoms			RR 95% CI			RR 95% CI
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

Outcome	ETS Exposure Low SpO2 Target	ETS Exposure High SpO2 Target	p-value	Without ETS Expsoure Low SpO2 Target	Without ETS Expsoure High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
			RR 95% CI			RR 95% CI
Respiratory Symptoms						
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

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School Age Breathing Outcomes

Modified ISAAC Questionnaire for 6/7 year olds

Enter name and relationship code of the person being interviewed*:

1a. Name: _____ _____ 1b. Relationship Code: |___|___|___|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here for other relationships, please look up relationship code from Appendix D of the Breathing Outcomes Manual of Operations and enter above.

2. Type of Interview: 1~ Face to Face 2~ Telephone

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Interview begins:

Some of these questions will be familiar to you.

In the past 12 months.....

3. How many times has your child visited a doctor's office?
None ☐
1-3 ☐
4-12 ☐
More than 12 ☐

3a. How many of these times were because of wheezing or breathing problems?
None ☐
1-3 ☐
4-12 ☐
More than 12 ☐

In the past 12 months .....

4. How many times has your child visited an Emergency Department (Emergency room)?
None ☐
1-3 ☐
4-12 ☐
More than 12 ☐

4a. How many of these times were because of wheezing or breathing problems?
None ☐
1-3 ☐
4-12 ☐
More than 12 ☐

In the past 12 months .....

5. How many times has your child stayed in the hospital one or more nights in a row?
None ☐
1-3 ☐
4-12 ☐
More than 12 ☐

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5a. How many of these times were because of wheezing or breathing problems?

- None ☐
- 1-3 ☐
- 4-12 ☐
- More than 12 ☐

Core questionnaire for wheezing

6. Has your child ever had wheezing or whistling in the chest at any time in the past?

- Yes ☐
- No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 11

7. Has your child had wheezing or whistling in the chest in the past 12 months?

- Yes ☐
- No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 11

8. How many attacks of wheezing has your child had in the past 12 months?

- None ☐
- 1 to 3 ☐
- 4 to 12 ☐
- More than 12 ☐

9. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

- Never woken with wheezing ☐
- Less than one night per week ☐
- One or more nights per week ☐

10. In the past 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

- Yes ☐
- No ☐

11. Has your child ever had asthma?

- Yes ☐
- No ☐

12. In the past 12 months, has your child's chest sounded wheezy during or after exercise?

- Yes ☐
- No ☐

13. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

- Yes ☐
- No ☐

14, Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?

- Yes ☐
- No ☐

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15. How much does your child weigh?: ☐ kg / stone / pounds
(please circle the measurement you used)

16. How tall is your child?: ☐ metres / centimetres / feet and inches
(please circle the measurement you used)

17. In the past 12 months, how often, on average, did your child eat or drink the following?: (Please leave blank if you do not know what a food is)

	Never or occasionally	Once or twice per week	Three or more times a week
Meat (e.g. beef, lamb, chicken, pork)	☐	☐	☐
Seafood (including fish)	☐	☐	☐
Fruit	☐	☐	☐
Vegetables (green and root)	☐	☐	☐
Pulses (peas, beans, lentils)	☐	☐	☐
Cereal (including bread)	☐	☐	☐
Pasta	☐	☐	☐
Rice	☐	☐	☐
Butter	☐	☐	☐
Margarine	☐	☐	☐
Nuts	☐	☐	☐
Potatoes	☐	☐	☐
Milk	☐	☐	☐
Eggs	☐	☐	☐
Fast food/burgers	☐	☐	☐

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18. How many times a week does your child engage in vigorous physical activity long enough to make him/her breathe hard?:

- Never or occasionally ☐
- Once or twice per week ☐
- Three or more times a week ☐

19. During a normal week, how many hours a **day (24hours)** does your child watch television?:

- Less than 1 hour ☐
- 1 hour but less than 3 hours ☐
- 3 hours but less than 5 hours ☐
- 5 hours or more ☐

20. In your house, what fuel is usually used for cooking?:

- Electricity ☐
- Gas ☐
- Open fires ☐
- Other – Please specify ☐

21. In your house, what fuel is usually used for heating?:

- Electricity ☐
- Gas, kerosene, paraffin ☐
- Wood, coal, oil ☐
- Other – Please specify ☐

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22. In the first 12 months of life, did your child have any antibiotics?:

Yes ☐

No ☐

23. How many older brothers and sisters does your child have?: ☐ brothers and sisters

24. How many younger brothers and sisters does your child have?: ☐ brothers and sisters

25. Was your child born in (NZ - See instructions)?:

Yes ☐

No ☐

26. How many years has your child lived in (NZ - see instructions)?: ☐ years

27. What level of education has the child's mother received?: (local wording)

Primary school ☐

Secondary school ☐

College, university or other form of tertiary education ☐

28. How often do trucks pass through the street where you live, on weekdays?:

Never ☐

Seldom ☐

Frequently through the day ☐

Almost the whole day ☐

29. Did you have a cat in your home during the first year of your child's life?:

Yes ☐

No ☐

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30. In the past 12 months, have you had a cat in your home?:

Yes ☐

No ☐

31. Did you have a dog in your home during the first year of your child's life?

Yes ☐

No ☐

32. In the past 12 months, have you had a dog in your home?: Yes ☐

No ☐

33. In your child's first year of life did he/she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)*?:

Yes ☐

No ☐

34. Has this child's Mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child?

Yes ☐

No ☐

35. Does your child's mother (or female guardian) smoke cigarettes?:

Yes ☐

No ☐

If **YES**, about how many cigarettes does the child's mother (or female guardian) smoke each day? ☐ number of cigarettes

36. Does your child's father (or male guardian) smoke cigarettes?:

Yes ☐

No ☐

If **YES**, about how many cigarettes does the child's father (or male guardian) smoke each day? ☐ number of cigarettes

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37. Did your child's mother (or female guardian) smoke cigarettes during your child's first year of life?:

Yes ☐

No ☐

38. How many people living in the house smoke cigarettes, people including parents?: ☐

OXYGEN

39. Since our last contact with you, has your child received oxygen therapy at home?
1~ Yes 2~ No *Skip to Question 41*

If yes to Questions 40

40a. Is your child currently on any oxygen therapy at home?
1~ Yes 2~ No *Skip to Question 41*

If yes, indicate Yes or No for each: *lpm = liters per minute

40b. Oxygen cannula	1~ Yes	2~ No	FiO2_____	lpm*_____
40c. Oxygen hood	1~ Yes	2~ No	FiO2_____	lpm*_____
40d. Ventilator	1~ Yes	2~ No	FiO2_____	lpm*_____

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MEDICATIONS *(Enter responses in table. Do not prompt for each medication in the Medication Code List below.)*

The next questions involve the medicines your child is taking for breathing problems.

40. Since our last contact with your, what medicines has your baby taken, including medicines taken by a nebulizer or breathing machine at home?	40a. Code	40b. Does he/she take that medicine everyday, sometimes or only when sick? *(repeat for each medication)*
1		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
2		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
3		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
4		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
5		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
6		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
7		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

Medication Code List:

***Rescue medicines*:**
1 Albuterol
2 Proventil
3 Serevent
4 Ventolin
5 Volmax
6 Xopenex

Other Inhaled medications:
7 Cromolyn (Intal)
8 Nedocromil (Tilade)

Inhaled steroids:
9 Advair
10 Aerobid
11 Azmacort
12 Beclovent
13 Flovent
14 Vanceril
15 Pulmicort

Systemic steroids:
16 Decadron
17 Prednisone
18 Prednisolone

Leukotriene blocker:
19 Accolate
20 Singulair

Methylxanthines:
21 Theophylline

Diuretic medications:
22 Diuril
23 Lasix
24 Aldactizide
25 Aldactone

Miscellaneous / Non-specific
26 Nebulizer
27
Other_____

Thank you very much for your help with this questionnaire. We appreciate your assistance.

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From: Gantz, Marie
To: Zaterka-Baxter, Kristin; david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call
Date: Wednesday, October 21, 2009 7:53:06 PM
Attachments: ROP adjudication data - ROP status unknown 21OCT09.pdf
MOP instructions for ROP data.pdf
SUPP10 ROP20071015.doc
NF05 Child Examination 1 16 2008.pdf

Attached are the following documents for the ROP adjudication call.

1) **ROP adjudication data – ROP status unknown 21OCT09.pdf** – This document contains data from ROP exams (form SUPP10) and 18 Month Follow-up (form NF05) for the 97 infants who survived to discharge and are missing the final ROP outcome.
2) **MOP instructions for ROP data.pdf** – This document contains instructions for completing the SUPP10 and vision-related items on NF05 from the SUPPORT and Follow-up Manuals of Operations.
3) Copies of SUPP10 and NF05 for reference.

Please let me know if you have any questions.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Zaterka-Baxter, Kristin
Sent: Wednesday, October 14, 2009 11:38 AM
To: 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call

Dear all,

We have scheduled a conference call for **Friday, October 23, 2009 from 4:00 = 5:00PM (EST)** to discuss a process to adjudicate cases with unclear ROP outcome. Contacts below:

Call in number: 1-866-675-(b) (6)
Pass code: (b) (6) (the "#" sign at the end is required)

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, October 12, 2009 2:48 PM
To: 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dear all,

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

Please let me know if you are willing and available this date and time.
Thanks,
Kris

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 1

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
1	991	27	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
1	1	1=Inpatient	4.9	32	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
1					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
1	2	1=Inpatient	7.1	34.3	Left	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
1					Right	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 2

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
2	1025	27	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
2	1	1=Inpatient	5.4	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
2					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
2	2	1=Inpatient	7	34.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
2					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
2	3	1=Inpatient	9.3	36.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
2					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
2	4	1=Inpatient	11.3	38.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
2					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
2	5	2=Outpatient	27.9	55.1	Left	9=Unable to determine	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
2					Right	9=Unable to determine	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
2	Left	2=No	2=No	2=No	1=Yes	1=Normal
2	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 3

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
3	962	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
3	1	1=Inpatient	4.9	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
3					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
3	2	1=Inpatient	7.3	34	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
3					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
3	3	2=Outpatient	10	36.7	Left	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
3					Right	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
3	Left	2=No	2=No	2=No	1=Yes	1=Normal
3	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 4

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
4	790	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
4	1	1=Inpatient	4.9	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
4					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
4	2	1=Inpatient	7.3	34	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
4					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
4	3	2=Outpatient	10	36.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
4					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
4	Left	2=No	2=No	2=No	1=Yes	1=Normal
4	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 5

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
5	790	26	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
5	1	1=Inpatient	5.7	32	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
5					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
5	2	1=Inpatient	7.9	34.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
5					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
5	3	1=Inpatient	9.1	35.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
5					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
5	4	1=Inpatient	12.1	38.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
5					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
5	5	2=Outpatient	16.9	43.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
5					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 6

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
6	806	26	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
6	1	1=Inpatient	5	31.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6	2	1=Inpatient	6.7	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6	3	1=Inpatient	8.7	35.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6	4	2=Outpatient	11.9	38.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
6					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 7

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
7	750	25	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
7	1	1=Inpatient	4.6	30.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7	2	1=Inpatient	5.6	31.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7	3	1=Inpatient	7.4	33.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7	4	1=Inpatient	10.3	36	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
7	5	2=Outpatient	12.9	38.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
7					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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Infant 8

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
8	990	27	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
8	1	1=Inpatient	4.7	32.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
8					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
8	2	1=Inpatient	6.9	34.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
8					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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Infant 9

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
9	800	27	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
9	1	1=Inpatient	3.9	30.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
9					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
9	2	1=Inpatient	6.6	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
9					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
9	3	1=Inpatient	8	35	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
9					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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Infant 10

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
10	945	26	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
10	1	1=Inpatient	5	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
10					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
10	2	1=Inpatient	6.4	33	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
10					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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Infant 11

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
11	800	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
11	1	1=Inpatient	5.4	32.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
11					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
11	2	1=Inpatient	7	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
11					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
11	3	1=Inpatient	9.4	36.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
11					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 12

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
12	595	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
12	1	1=Inpatient	7	32.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12	2	1=Inpatient	8.9	34.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12	3	1=Inpatient	10.7	36.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
12	4	1=Inpatient	13.7	39.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
12					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS
Infant 13

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
13	1025	27	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
13	1	1=Inpatient	5	32.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
13					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
13	2	1=Inpatient	6.9	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
13					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
13	3	1=Inpatient	36.7	64.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
13					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
13	Left	2=No	2=No	2=No	1=Yes	1=Normal
13	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 14

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
14	950	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
14	1	1=Inpatient	6.4	32.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14					Right	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14	2	1=Inpatient	7.3	33.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14	3	1=Inpatient	9.3	35.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
14	4	1=Inpatient	11.3	37.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
14					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
14	5	1=Inpatient	13.1	39.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
14					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
14	6	2=Outpatient	52.1	78.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
14					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
14	Left	2=No	2=No	2=No	1=Yes	1=Normal
14	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 15

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
15	700	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
15	1	1=Inpatient	5.6	33	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
15					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
15	2	1=Inpatient	7.6	35	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15	3	1=Inpatient	8.4	35.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15	4	1=Inpatient	9.6	37	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
15	5	1=Inpatient	11.7	39.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15					Right	2=II	1=Stage 1	3=Stage 3	N	N	0=No surgery	0=None
15	6	1=Inpatient	12.3	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15	7	1=Inpatient	13.4	40.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15	8	1=Inpatient	15.6	43	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
15	9	1=Inpatient	17.6	45	Left	1=I	3=Stage 3	3=Stage 3	*	*	.	.
15					Right	1=I	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
15	10	2=Outpatient	40.3	67.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
15					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
15	Left	2=No	2=No	2=No	1=Yes	1=Normal
15	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 16

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
16	675	24	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
16	1	1=Inpatient	8.9	32.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
16					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
16	2	1=Inpatient	10	34	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
16					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
16	3	1=Inpatient	10.7	34.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
16					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
16	4	1=Inpatient	11.9	35.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
16					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
16	5	1=Inpatient	13.9	37.9	Left	3=III	.	.	N	N	0=No surgery	0=None
16					Right	3=III	.	.	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 17

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
17	1140	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
17	1	1=Inpatient	4.4	31.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
17					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
17	2	1=Inpatient	5.4	32.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
17					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
17	3	1=Inpatient	6.4	33.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
17					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
17	4	1=Inpatient	7.4	34.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
17					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
17	5	1=Inpatient	9.4	36.9	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
17					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
17	Left	2=No	2=No	2=No	1=Yes	1=Normal
17	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 18

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
18	1140	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
18	1	1=Inpatient	5.9	33.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
18					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
18	2	1=Inpatient	8	35.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
18					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
18	3	2=Outpatient	10	37.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
18					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 19

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
19	655	24	4	Y

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 20

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
20	940	25	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
20	1	1=Inpatient	5.6	31.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
20					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
20	2	1=Inpatient	7.6	33.3	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
20					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 21

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
21	990	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
21	1	1=Inpatient	4.9	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
21					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
21	2	1=Inpatient	7	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
21					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
21	3	1=Inpatient	9	36.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
21					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 22

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
22	590	24	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
22	1	1=Inpatient	5.9	30.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
22					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
22	2	1=Inpatient	7	31.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
22					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
22	3	1=Inpatient	9	33.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
22					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
22	4	1=Inpatient	9.9	34.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
22					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
22	5	1=Inpatient	10.9	35.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
22					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
22	6	1=Inpatient	12	36.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
22					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
22	7	1=Inpatient	13	37.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
22					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
23	860	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
23	1	1=Inpatient	7	32.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
23					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
23	2	1=Inpatient	7.9	33.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
23					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
23	3	1=Inpatient	9.9	35.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
23					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 24

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
24	790	25	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
24	1	1=Inpatient	6.7	32.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
24					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24	2	1=Inpatient	7.9	33.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24	3	1=Inpatient	8.9	34.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24	4	1=Inpatient	9.9	35.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24	5	1=Inpatient	11.7	37.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	.
24					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
24	6	1=Inpatient	13.6	39	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
24					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.
24	7	1=Inpatient	16.7	42.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
24					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 25

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
25	1330	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
25	1	1=Inpatient	8.9	36.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.
25					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	.

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Infant 26

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
26	1030	26	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
26	1	1=Inpatient	7.6	33.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
26					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 27

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
27	770	25	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
27	1	1=Inpatient	7	32	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
27	2	1=Inpatient	8.9	33.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27	3	1=Inpatient	10.9	35.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27	4	2=Outpatient	14.4	39.4	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
27					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 28

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
28	900	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
28	1	1=Inpatient	5.9	33.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
28					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
28	Left	2=No	2=No	2=No	1=Yes	1=Normal
28	Right	2=No	2=No	2=No	1=Yes	1=Normal

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
29	1000	26	.	Y

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
29	Left	2=No	2=No	2=No	1=Yes	1=Normal
29	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 30

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
30	940	27	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
30	1	1=Inpatient	6.1	33.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
30					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
30	2	1=Inpatient	8.3	35.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
30					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
30	3	1=Inpatient	10.1	37.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
30					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
30	Left	2=No	2=No	2=No	1=Yes	1=Normal
30	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 31

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
31	940	25	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
31	1	1=Inpatient	7.1	32.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31	2	1=Inpatient	9.3	34.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31	3	1=Inpatient	11.1	36.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31	4	2=Outpatient	13.9	38.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31	5	2=Outpatient	16.1	41.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31	6	2=Outpatient	18.3	43.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
31					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
31	Left	2=No	2=No	2=No	2=No	1=Normal
31	Right	2=No	2=No	2=No	2=No	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 32

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
32	810	25	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
32	1	1=Inpatient	9.6	35.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
32					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
32	2	1=Inpatient	11.4	37.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
32					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 33

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
33	800	24	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
33	1	1=Inpatient	6.1	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
33					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
33	2	1=Inpatient	7.1	32	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
33					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
33	3	1=Inpatient	10.1	35	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33	4	1=Inpatient	12.1	37	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33	5	1=Inpatient	15.1	40	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33	6	1=Inpatient	16.7	41.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33	7	1=Inpatient	19.7	44.6	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
33					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
33	Left	2=No	2=No	2=No	1=Yes	1=Normal
33	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 34

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
34	760	26	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
34	1	3=TF hospital	6.4	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
34					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
34	2	3=TF hospital	8.9	35.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
34					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 35

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
35	980	25	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
35	1	1=Inpatient	5.7	31.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
35					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
35	2	1=Inpatient	7.6	33.3	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35	3	1=Inpatient	10.7	36.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35	4	3=TF hospital	12.7	38.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
35	5	2=Outpatient	30	55.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
35					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
35	Left	2=No	2=No	2=No	1=Yes	1=Normal
35	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 36

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
36	840	25	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
36	1	1=Inpatient	5.9	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
36					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
36	2	1=Inpatient	8	33.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	3	1=Inpatient	9.1	34.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	4	1=Inpatient	11.1	36.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	5	2=Outpatient	13.3	38.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	6	2=Outpatient	15.3	40.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	7	2=Outpatient	17.3	42.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36	8	2=Outpatient	19.3	44.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36	9	2=Outpatient	21	46.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36	10	2=Outpatient	23.1	48.3	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36	11	2=Outpatient	28.3	53.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
36	12	2=Outpatient	42.3	67.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
36					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
36	13	2=Outpatient	69.3	94.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
36					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
36	Left	2=No	2=No	2=No	1=Yes	1=Normal
36	Right	2=No	2=No	2=No	1=Yes	1=Normal

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
37	780	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
37	1	1=Inpatient	5.9	31.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
37					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
37	2	1=Inpatient	7.7	33.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37	3	1=Inpatient	9.7	35.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
37	4	1=Inpatient	11.7	37.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37	5	2=Outpatient	13.9	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37	6	2=Outpatient	16	41.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37	7	2=Outpatient	18	43.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
37	8	2=Outpatient	24.4	50.3	Left	See F5	.	.	*	*	.	.
37					Right	.	.	.	*	*	.	.
37	9	2=Outpatient	38.9	64.7	Left	See F5	.	.	*	*	.	.
37					Right	.	.	.	*	*	.	.

F5 (Comment from center) for exams 8 & 9: "Pt too large for depressed retinal exam. Macula is flat & attached."

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
37	Left	2=No	2=No	2=No	1=Yes	1=Normal
37	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 38

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
38	730	24	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
38	1	1=Inpatient	5.9	30	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
38					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
38	2	1=Inpatient	7.9	32	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
38					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38	3	3=TF hospital	10.3	34.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
38					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
38	4	3=TF hospital	12.3	36.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
38	5	1=Inpatient	12.4	36.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
38	6	1=Inpatient	13	37.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38	7	1=Inpatient	13.9	38	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
38	8	2=Outpatient	16.4	40.6	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
38					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
38	9	2=Outpatient	17.4	41.6	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
38					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
38	10	2=Outpatient	20	44.1	Left	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
38					Right	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
38	Left	2=No	2=No	2=No	1=Yes	1=Normal
38	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 39

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
39	490	24	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
39	1	1=Inpatient	5.3	29.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
39					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
39	2	1=Inpatient	7.6	32	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	3	1=Inpatient	9.4	33.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
39	4	1=Inpatient	10.4	34.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	5	1=Inpatient	12.3	36.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	6	1=Inpatient	14.4	38.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	7	1=Inpatient	16.3	40.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	8	2=Outpatient	18.7	43.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	9	2=Outpatient	20.7	45.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
39	10	2=Outpatient	46.7	71.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
39					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
39	Left	2=No	2=No	2=No	1=Yes	1=Normal
39	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 40

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
40	990	26	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
40	1	1=Inpatient	4.6	31.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
40					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
40	2	1=Inpatient	5.6	32.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40	3	1=Inpatient	6.6	33.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40	4	1=Inpatient	8.4	35.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40	5	2=Outpatient	10.9	37.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40	6	2=Outpatient	12.9	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40	7	2=Outpatient	15.4	42.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
40	8	2=Outpatient	17.9	44.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
40					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
40	9	2=Outpatient	20.9	47.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
40					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
40	10	2=Outpatient	23.9	50.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
40					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
40	11	2=Outpatient	50.7	77.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
						See F5						
40					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
						See F5						

F5 (Comment from center) for exam 11 left and right eye lowest zone: "Per physician, eyes to never vascularize fully."

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
40	Left	2=No	2=No	2=No	1=Yes	1=Normal
40	Right	2=No	2=No	2=No	1=Yes	1=Normal

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
41	835	26	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
41	1	1=Inpatient	7	33	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41	2	1=Inpatient	9.3	35.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41	3	2=Outpatient	11.1	37.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41	4	2=Outpatient	13.7	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41	5	2=Outpatient	15.7	41.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
41					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
41	Left	2=No	2=No	2=No	1=Yes	1=Normal
41	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS
Infant 42

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
42	900	26	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
42	1	1=Inpatient	4.9	31.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
42					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
42	2	1=Inpatient	7.3	33.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42	3	1=Inpatient	10.6	36.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42	4	1=Inpatient	12.1	38.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42	5	2=Outpatient	14.3	40.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
42	6	2=Outpatient	16.3	42.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42	7	2=Outpatient	18.3	44.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42	8	2=Outpatient	39.3	65.6	Left	2=II See F5	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
42					Right	2=II See F5	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

F5 (Comment from center) for exam 8 left and right eye lowest zone: "Per physician, eyes will never mature."

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
42	Left	2=No	2=No	2=No	1=Yes	1=Normal
42	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS
Infant 43

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
43	740	25	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
43	1	1=Inpatient	5.7	30.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
43					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
43	2	1=Inpatient	7.4	32.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
43					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
43	3	1=Inpatient	9.4	34.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
43					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 44

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
44	890	26	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
44	1	1=Inpatient	5.7	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
44					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
44	2	1=Inpatient	7.6	34.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
44					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 45

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
45	850	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
45	1	1=Inpatient	5.3	31.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
45					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
45	2	1=Inpatient	7.3	33.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	3	1=Inpatient	8.4	34.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	4	1=Inpatient	9.4	35.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	5	2=Outpatient	10.3	36.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	6	2=Outpatient	11.7	37.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	7	2=Outpatient	13.3	39.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	8	2=Outpatient	14.4	40.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	9	2=Outpatient	15.7	41.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	10	2=Outpatient	17.3	43.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
45	11	2=Outpatient	18.7	44.6	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
45					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
45	12	2=Outpatient	20.7	46.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
45					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
45	13	2=Outpatient	24.7	50.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
45					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 46

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
46	920	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
46	1	1=Inpatient	5.3	31.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
46					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
46	2	1=Inpatient	7.3	33.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	3	1=Inpatient	8.4	34.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	4	1=Inpatient	9.4	35.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	5	2=Outpatient	10.3	36.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
46					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
46	6	2=Outpatient	11.7	37.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	7	2=Outpatient	13.3	39.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
46					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
46	8	2=Outpatient	14.4	40.3	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
46					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
46	9	2=Outpatient	15.7	41.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	10	2=Outpatient	17.3	43.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
46	11	2=Outpatient	18.7	44.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
46					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 47

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
47	400	24	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
47	1	1=Inpatient	5.6	29.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
47					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
47	2	1=Inpatient	7.7	31.9	Left	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47					Right	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47	3	1=Inpatient	8.7	32.9	Left	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47					Right	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47	4	1=Inpatient	9.6	33.7	Left	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47					Right	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47	5	1=Inpatient	10.6	34.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	6	1=Inpatient	12.6	36.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	7	1=Inpatient	13.6	37.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	8	1=Inpatient	14.7	38.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	9	1=Inpatient	15.7	39.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	10	1=Inpatient	16.7	40.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	11	1=Inpatient	17.7	41.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	12	1=Inpatient	18.9	43	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
47					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
47	13	1=Inpatient	19.9	44	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
47					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
47	14	1=Inpatient	21	45.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	15	1=Inpatient	23	47.1	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
47	16	2=Outpatient	25.6	49.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
47					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 48

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
48	900	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
48	1	1=Inpatient	5.4	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
48					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
48	2	1=Inpatient	7.6	33.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
48					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
48	3	1=Inpatient	10.3	36.4	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
48					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 49

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
49	500	24	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
49	1	1=Inpatient	7.9	32.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
49					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
49	2	1=Inpatient	9.9	34.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
49					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
49	3	1=Inpatient	11.4	35.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
49					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49	4	1=Inpatient	12.4	36.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
49					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49	5	1=Inpatient	13.4	37.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
49					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49	6	3=TF hospital	15	39.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49	7	2=Outpatient	17.4	41.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
49					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 50

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
50	810	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
50	1	1=Inpatient	6.1	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
50					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
50	2	3=TF hospital	9.9	36	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
50					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
50	3	3=TF hospital	7.9	34	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
50					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
50	4	3=TF hospital	11.3	37.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
50					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
50	5	2=Outpatient	14.3	40.4	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
50					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 51

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
51	830	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
51	1	1=Inpatient	6.9	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
51					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
51	2	1=Inpatient	9	35.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
51					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 52

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
52	1180	27	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
52	1	1=Inpatient	5	32.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52	2	1=Inpatient	7	34.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52	3	1=Inpatient	9	36.6	Left	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
52	4	1=Inpatient	10.7	38.3	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
52					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
52	5	2=Outpatient	13.1	40.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
52					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 53

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
53	830	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
53	1	1=Inpatient	3.9	31.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53	2	1=Inpatient	5.7	33.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53	3	3=TF hospital	6.9	34.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53	4	3=TF hospital	8.9	36.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53	5	2=Outpatient	10.9	38.3	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
53					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 54

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
54	900	26	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
54	1	1=Inpatient	3.7	30.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
54					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
54	2	1=Inpatient	5.7	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
54					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
54	3	1=Inpatient	7.7	34.3	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
54					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 55

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
55	735	26	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
55	1	1=Inpatient	5.9	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
55					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
55	2	1=Inpatient	6.9	33.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
55					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
55	3	1=Inpatient	7.9	34.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
55					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
55	4	1=Inpatient	9.9	36.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
55					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
55	5	1=Inpatient	11.9	38.7	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
55					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
56	1100	27	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
56	1	1=Inpatient	5.4	32.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
56					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
56	Left	2=No	2=No	2=No	1=Yes	1=Normal
56	Right	2=No	2=No	2=No	1=Yes	1=Normal

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
57	660	27	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
57	1	1=Inpatient	5.9	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
57					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
57	2	1=Inpatient	7	34.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
57					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
57	3	1=Inpatient	9	36.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
57					Right	9=Unable to determine See F5	.	.	*	*	.	.
57	4	1=Inpatient	11	38.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57	5	1=Inpatient	12	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57	6	1=Inpatient	14	41.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57	7	1=Inpatient	16	43.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57	8	1=Inpatient	17	44.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
57					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

F5 (Comment from center) for exam 3: "Stopped due to instability."

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
57	Left	2=No	2=No	2=No	1=Yes	1=Normal
57	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 58

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
58	1190	27	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
58	1	1=Inpatient	2.4	30.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
58					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
58	2	1=Inpatient	5	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
58					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
58	Left	2=No	2=No	2=No	1=Yes	1=Normal
58	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 59

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
59	480	25	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
59	1	1=Inpatient	6.9	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59	2	1=Inpatient	8.7	34.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59	3	1=Inpatient	10.4	36.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59	4	1=Inpatient	12.7	38.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
59					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
59	Left	2=No	2=No	2=No	1=Yes	1=Normal
59	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 60

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
60	810	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
60	1	1=Inpatient	6.7	34.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
60					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
60	2	1=Inpatient	8.6	36.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
60					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
61	760	24	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
61	1	1=Inpatient	5.4	30.3	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61	2	1=Inpatient	7.7	32.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61	3	1=Inpatient	9.6	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
61	4	1=Inpatient	11.3	36.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
61					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 62

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
62	580	25	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
62	1	1=Inpatient	5.1	30.7	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
62					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
62	2	1=Inpatient	7	32.6	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
62					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
62	3	1=Inpatient	8.9	34.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
62					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
62	4	1=Inpatient	10.7	36.3	Left	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
62					Right	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 63

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
63	1050	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
63	1	1=Inpatient	5.7	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
63					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
63	2	1=Inpatient	7.3	35.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
63					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
63	3	1=Inpatient	9.6	37.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
63					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
63	4	1=Inpatient	11.1	39	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
63					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 64

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
64	740	25	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
64	1	1=Inpatient	8.1	33.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64	2	1=Inpatient	9	34.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64	3	1=Inpatient	10.1	35.7	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64	4	1=Inpatient	14.1	39.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
64					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
64	5	1=Inpatient	17.3	42.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
64					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 65

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
65	1265	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
65	1	1=Inpatient	5.1	32.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
65					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
65	2	1=Inpatient	7.1	34.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
65					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
65	3	2=Outpatient	11.1	38.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
65					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION: INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 66

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
66	1200	27	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
66	1	1=Inpatient	6.7	33.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
66					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
67	928	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
67	1	1=Inpatient	3.7	29.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67	2	1=Inpatient	4.9	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67	3	1=Inpatient	5.9	32	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67	4	1=Inpatient	7.9	34	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67	5	1=Inpatient	10.9	37	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
67					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
67	Left	2=No	2=No	2=No	1=Yes	1=Normal
67	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
68	1075	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
68	1	1=Inpatient	4.4	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
68					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
68	2	1=Inpatient	6.4	34.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
68					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
68	3	2=Outpatient	60.7	88.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
68					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
68	Left	2=No	2=No	2=No	1=Yes	1=Normal
68	Right	2=No	2=No	2=No	1=Yes	1=Normal

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Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
69	540	24	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
69	1	1=Inpatient	6.6	30.7	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	2	1=Inpatient	7	31.1	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	3	1=Inpatient	7.6	31.7	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	4	1=Inpatient	8	32.1	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	5	1=Inpatient	8.6	32.7	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	6	1=Inpatient	9	33.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	7	1=Inpatient	9.6	33.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	8	1=Inpatient	10	34.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	9	1=Inpatient	10.6	34.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	10	1=Inpatient	11	35.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	11	1=Inpatient	11.7	35.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	12	1=Inpatient	12.6	36.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	13	1=Inpatient	13.6	37.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	14	1=Inpatient	14.6	38.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	15	1=Inpatient	15.7	39.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69	16	1=Inpatient	16.7	40.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
69					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 69

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
69	17	2=Outpatient	61.9	86	Left	3=III	3=Stage 3	3=Stage 3	Y	N	0=No surgery	0=None
69					Right	3=III	3=Stage 3	3=Stage 3	Y	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
69	Left	2=No	2=No	2=No	1=Yes	1=Normal
69	Right	2=No	2=No	2=No	1=Yes	2=Corrective lenses

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 70

Infant*	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
70	1040	27	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
70	1	1=Inpatient	4.4	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
70					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
70	2	1=Inpatient	6.6	33.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
70					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
70	3	1=Inpatient	7.6	34.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
70					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

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Infant 71

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
71	1010	27	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
71	1	1=Inpatient	4.3	31.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71	2	1=Inpatient	6.3	33.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71	3	1=Inpatient	8.3	35.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71	4	2=Outpatient	10.4	38	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
71					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
71	Left	2=No	2=No	2=No	1=Yes	1=Normal
71	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 72

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
72	825	26	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
72	1	1=Inpatient	4.6	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
72					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
72	2	1=Inpatient	6.4	32.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	3	1=Inpatient	7.6	34	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	4	1=Inpatient	8.6	35	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	5	1=Inpatient	9.6	36	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	6	1=Inpatient	10.6	37	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	7	1=Inpatient	11.6	38	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	8	1=Inpatient	12.6	39	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	9	1=Inpatient	13.6	40	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	10	2=Outpatient	16.3	42.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72	11	2=Outpatient	20.3	46.7	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
72					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
72	Left	2=No	2=No	2=No	1=Yes	1=Normal
72	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 73

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
73	545	25	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
73	1	1=Inpatient	6.7	32.3	Left	.	.	.	*	*	.	.
73					Right	.	.	.	*	*	.	.
73	2	1=Inpatient	7.9	33.4	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	.
73					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	.
73	3	1=Inpatient	8.7	34.3	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73	4	1=Inpatient	9.7	35.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73	5	1=Inpatient	10.7	36.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73	6	1=Inpatient	11.7	37.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
73	7	1=Inpatient	12.7	38.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	8	1=Inpatient	13.7	39.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	9	1=Inpatient	15.1	40.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	10	1=Inpatient	15.9	41.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	11	1=Inpatient	16.7	42.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	12	1=Inpatient	17.7	43.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	13	1=Inpatient	18.7	44.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	14	1=Inpatient	20.7	46.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73	15	2=Outpatient	59.4	85	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
73					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
73	Left	1=Yes	1=Yes	2=No	1=Yes	3=Other abnormality
73	Right	1=Yes	1=Yes	2=No	1=Yes	3=Other abnormality

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DATA FOR ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 74

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
74	455	24	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
74	1	1=Inpatient	7.6	32	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	2	1=Inpatient	8.9	33.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	3	1=Inpatient	9.7	34.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	4	1=Inpatient	10.6	35	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	5	1=Inpatient	11.6	36	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	6	1=Inpatient	13.6	38	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	7	1=Inpatient	15.6	40	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	8	1=Inpatient	17.6	42	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74	9	2=Outpatient	20.3	44.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
74					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
74	Left	2=No	2=No	2=No	1=Yes	1=Normal
74	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 75

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
75	1095	26	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
75	1	1=Inpatient	6.6	33.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
75					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
75	2	1=Inpatient	7.6	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
75					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
75	3	1=Inpatient	9.6	36.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
75					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
75	4	1=Inpatient	11.6	38.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
75					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
75	5	2=Outpatient	14.3	41.1	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
75					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
76	770	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
76	1	1=Inpatient	5.7	32.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
76					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
76	2	1=Inpatient	7.7	34.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
76					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
76	3	1=Inpatient	8.9	35.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
76					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
76	4	1=Inpatient	10.7	37.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
76					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
76	5	1=Inpatient	12.9	39.6	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
76					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
77	755	27	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
77	1	1=Inpatient	5.9	33.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
77					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
77	2	1=Inpatient	8	35.9	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
77					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 78

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
78	1150	27	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
78	1	1=Inpatient	4	31.7	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78	2	1=Inpatient	6.1	33.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78	3	1=Inpatient	8	35.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78	4	1=Inpatient	10.1	37.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78	5	1=Inpatient	12.1	39.9	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
78					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 79

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
79	730	25	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
79	1	1=Inpatient	6	31.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79	2	1=Inpatient	7.1	32.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79	3	1=Inpatient	10	35.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79	4	1=Inpatient	12	37.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79	5	1=Inpatient	14	39.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79	6	2=Outpatient	15.7	41.4	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
79					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 80

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
80	840	25	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
80	1	1=Inpatient	6.7	31.7	Left	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80					Right	1=I	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80	2	1=Inpatient	7.6	32.6	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80	3	1=Inpatient	8.7	33.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80	4	1=Inpatient	10	35	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
80	5	1=Inpatient	12.7	37.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
80					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 81

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
81	995	27	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
81	1	1=Inpatient	4.9	32.4	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
81					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
81	2	1=Inpatient	6.7	34.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
81					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
81	3	1=Inpatient	8.7	36.3	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
81					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 82

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
82	850	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
82	1	1=Inpatient	5.7	31.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82	2	1=Inpatient	7.6	33.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82	3	1=Inpatient	9.6	35.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82	4	2=Outpatient	13.3	39.4	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
82					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 83

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
83	1100	27	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
83	1	1=Inpatient	5.7	32.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
83					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
83	2	1=Inpatient	7.7	34.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
83					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
83	3	2=Outpatient	9.9	37	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
83					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 84

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
84	950	27	3	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
84	1	1=Inpatient	6.3	33.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	.
84					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
84	2	1=Inpatient	8.1	35.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
84					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
84	3	2=Outpatient	11.3	38.7	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
84					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 85

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
85	725	25	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
85	1	1=Inpatient	2.9	28.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85	2	1=Inpatient	5.9	31.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85	3	1=Inpatient	6.9	32.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
85	4	1=Inpatient	7.9	33.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
85					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
85	5	1=Inpatient	8.9	34.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
85					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
85	6	1=Inpatient	9.9	35.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	7	1=Inpatient	10.9	36.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	8	1=Inpatient	11.9	37.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	9	1=Inpatient	13.1	38.4	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	10	1=Inpatient	13.9	39.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	11	1=Inpatient	14.9	40.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	12	1=Inpatient	15.9	41.1	Left	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85					Right	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
85	13	2=Outpatient	18	43.3	Left	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
85					Right	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 86

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
86	580	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
86	1	1=Inpatient	6.4	33.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86	2	1=Inpatient	7.4	34.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86	3	1=Inpatient	8.4	35.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86					Right	1=I	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86	4	1=Inpatient	9.4	36.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86	5	1=Inpatient	11.4	38.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
86					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
86	6	1=Inpatient	13.4	40.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86	7	1=Inpatient	15.4	42.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
86					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86	8	1=Inpatient	17.4	44.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
86	9	1=Inpatient	19.4	46.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
86					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS
Infant 87

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
87	760	27	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
87	1	3=TF hospital	4.6	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
87					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
87	2	3=TF hospital	7.6	34.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
87					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
87	Left	2=No	2=No	2=No	1=Yes	1=Normal
87	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 88

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
88	800	24	6	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
88	1	1=Inpatient	4.7	29.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
88					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
88	2	1=Inpatient	6.7	31.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
88					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
88	3	1=Inpatient	8.7	33.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
88					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
88	4	1=Inpatient	9.7	34.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
88					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
88	5	1=Inpatient	10.7	35.6	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
88					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 89

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
89	657	24	2	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
89	1	1=Inpatient	7.1	31.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89	2	1=Inpatient	8.1	32.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	3	1=Inpatient	9.1	33.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	4	1=Inpatient	10.1	34.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	5	1=Inpatient	11.1	35.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	6	1=Inpatient	12.1	36.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	7	1=Inpatient	13.1	37.4	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	8	1=Inpatient	14	38.3	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
89	9	2=Outpatient	15.1	39.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89	10	2=Outpatient	16	40.3	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89	11	2=Outpatient	17.1	41.4	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
89					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 90

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
90	927	26	0	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
90	1	1=Inpatient	5.7	31.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	2	1=Inpatient	6.7	32.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	3	1=Inpatient	7.6	33.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	4	1=Inpatient	8.7	34.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	5	1=Inpatient	9.7	35.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	6	1=Inpatient	10.7	36.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	7	1=Inpatient	12.9	38.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90	8	1=Inpatient	13.7	39.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
90					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 91

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
91	975	25	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
91	1	1=Inpatient	0.1	25.7	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	2	1=Inpatient	1.3	26.9	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	3	1=Inpatient	2.3	27.9	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	4	1=Inpatient	3.3	28.9	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	5	1=Inpatient	3.9	29.4	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	6	1=Inpatient	4.4	30	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	7	1=Inpatient	5.4	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	8	1=Inpatient	6.3	31.9	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91	9	1=Inpatient	7.3	32.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91	10	1=Inpatient	8.3	33.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91	11	2=Outpatient	9.3	34.9	Left	1=I	1=Stage 1	0=No ROP	N	N	0=No surgery	0=None
91					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91	12	1=Inpatient	10.3	35.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91	13	1=Inpatient	11.3	36.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91	14	2=Outpatient	13.1	38.7	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91	15	2=Outpatient	14.3	39.9	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
91					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
91	16	2=Outpatient	18.4	44	Left	2=II	1=Stage 1	.	N	N	.	.
91					Right	2=II	1=Stage 1	1=Stage 1	N	N	.	.
91	17	2=Outpatient	20.4	46	Left	2=II	1=Stage 1	1=Stage 1	N	N	.	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 91

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
91					Right	2=II	1=Stage 1	1=Stage 1	N	N	.	.
91	18	2=Outpatient	23.4	49	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
91					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 92

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
92	866	26	5	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
92	1	1=Inpatient	4.4	31.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92	2	1=Inpatient	5.6	32.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92	3	1=Inpatient	7.6	34.3	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92	4	1=Inpatient	8.4	35.1	Left	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92					Right	1=I	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92	5	1=Inpatient	9.6	36.3	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
92	6	2=Outpatient	11.9	38.6	Left	1=I	0=No ROP	1=Stage 1	N	N	0=No surgery	0=None
92					Right	2=II	0=No ROP	1=Stage 1	N	N	0=No surgery	0=None
92	7	2=Outpatient	12.7	39.4	Left	3=III	0=No ROP	0=No ROP	N	N	.	.
92					Right	3=III	0=No ROP	0=No ROP	N	N	.	.

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 93

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
93	741	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
93	1	1=Inpatient	4.9	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93	2	1=Inpatient	6.9	33	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93	3	1=Inpatient	8.9	35	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93	4	1=Inpatient	10.9	37	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93	5	2=Outpatient	13	39.1	Left	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
93					Right	3=III	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
93	Left	2=No	2=No	2=No	1=Yes	1=Normal
93	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 94

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
94	748	26	1	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
94	1	1=Inpatient	4.9	31	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94	2	1=Inpatient	6.9	33	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94	3	1=Inpatient	8.9	35	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94	4	1=Inpatient	9.4	35.6	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94	5	2=Outpatient	13	39.1	Left	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None
94					Right	2=II	0=No ROP	0=No ROP	N	N	0=No surgery	0=None

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
94	Left	2=No	2=No	2=No	1=Yes	1=Normal
94	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 95

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
95	1000	25	5	Y

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
95	1	2=Outpatient	132.6	158.3	Left	.	.	.	*	*	.	.
95					Right	.	.	.	*	*	.	.

Infant	FU exam: Eye	Strabismus	Nystagmus	Roving eye movements	Tracks 180 degrees	Vision
95	Left	2=No	2=No	2=No	1=Yes	1=Normal
95	Right	2=No	2=No	2=No	1=Yes	1=Normal

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DATA FOR ROP AD JUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
96	740	24	4	N

Infant	SUPP10 exam	Location	Age (weeks)	PMA (weeks)	Eye	Lowest zone of any vessels	Highest stage in lowest zone	Highest stage in any zone	Plus disease	Threshold	Surgery	Post-surgical retinal detachment
96	1	1=Inpatient	8.6	33.1	Left	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
96					Right	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery	0=None
96	2	1=Inpatient	9.3	33.9	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96	3	1=Inpatient	10.6	35.1	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96	4	1=Inpatient	11.4	36	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96	5	1=Inpatient	12.6	37.1	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96	6	1=Inpatient	13.6	38.1	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96	7	1=Inpatient	14.7	39.3	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96	8	1=Inpatient	15.6	40.1	Left	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery	0=None
96	9	1=Inpatient	17.9	42.4	Left	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96					Right	2=II	2=Stage 2	3=Stage 3	N	N	0=No surgery	0=None
96	10	2=Outpatient	18.4	43	Left	3=III	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None
96					Right	3=III	3=Stage 3	3=Stage 3	N	N	0=No surgery	0=None

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DATA FOR ROP ADJUDICATION - INFANTS WITH UNKNOWN FINAL ROP STATUS

Infant 97

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)	Infant was withdrawn from study
97	550	24	2	Y

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Instructions for SUPPORT Form SUPP10: ROP Outcomes and Tracking (From the SUPPORT Manual of Operations)

The purpose of this form is to track and document the acute ROP outcome of each eye. Tracking the course of ROP should begin with the first examination and will generally be much easier if the coordinator attends the examinations and asks the ophthalmologist in person about the categories to be recorded.

Data may be entered in the database from the form after each examination, or may be entered when the infant reaches "acute/final" status. However, monitoring of the examinations and progress will be much more complete and helpful if these are entered after each examination.

Complete this form for all enrollees in SUPPORT who survive to have their first eye examination. This normally is scheduled at 31 weeks postmenstrual age (but not earlier than 4 weeks after birth).

Record the data for each eye examination until each eye has reached "acute/final" status (see definition below in 15.2). This will sometimes include examinations following discharge home or transfer to another hospital.

1. **Date of Exam**
   If a confirming examination is conducted, each should be separately recorded.

2. **Location of Exam**
   Code 1= inpatient for the primary hospital where the infant has been cared for, including other Units in that same hospital (step down units, pediatric intensive care, surgical care units, etc.)

   Code 2=Outpatient for examinations in the outpatient ophthalmology department, private ophthalmologist's office or other outpatient visits. Include infants at a chronic care facility transported to the physician's office for an examination.

   Code 3= Transfer Hospital when infants have been back transferred to a referring hospital or regional hospital.

   Note: Outpatient and back transfer hospitals can be a common source of infants missing examinations and "slipping through the cracks". Be particularly attentive to ensuring timely repeat examinations in these cases and ensure that the family is aware of the importance and critical timing of the examinations.

3. **Lowest zone:** Record the lowest zone that contains vessels that end before crossing out of that zone. This may be zone I (the most immature), zone II (intermediate) or zone III (most mature). The ophthalmologist normally records this on the eye examination form. The most common for SUPPORT infants will be zone II at the early examinations. There may be vessels recorded in:
   - zone I and II (you record zone I)
   - zone I only (you record zone I)
   - zone II only (you record zone II)
   - zone III only (you record zone III)

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Note that by convention, disease is never to be recorded in zones II and III in the same eye. If the two nasal clock-hours are not fully vascularized, by convention, no vessels in that eye are to be recorded in zone III. If they are fully vascularized, the all the rest of that eye's vessels are in zone III.

4. **Highest stage in lowest zone** (not to be used if eye has had surgery)
Look first at the lowest zone that has vessels ending in it (see previous answer). Then look to see if there is ROP in any of the clock hours of that zone. Choose the highest stage of ROP in that zone to record.

Examples:

If the eye has vessels ending in just zone I, but no ROP, the highest stage is zero.

If the eye has vessels ending in zone I and zone II and the ROP in zone I is stage 2 while the ROP in zone II is stage 3, the highest stage in the lowest zone (I) is stage 2.

If the eye has vessels ending in zone I, but there is no ROP in zone I, but there is stage 2 and stage 3 ROP in zone II, the answer would be 0=no ROP in the lowest zone.

5. **Highest stage in any zone** (not to be used if eye has had surgery)
Look at the stage of ROP around the 12 clock-hours of the recorded examination. Choose the highest stage to record. In rank order going from lowest to highest the order is 0, 1, 2, 3, 4a, 4b, 5. The other categories are for less common cases.
- Code 4 = stage 4a or 4b is a partial retinal detachment
- Code 5 = stage 5 which is a total retinal detachment
- Code 6 = Post laser/cyro (do not use stages)
- Code 9 = Old scars, but no active ROP

6. **"Plus disease"**
This is recorded by the ophthalmologist as present or not. Sometimes they provide comments like 'borderline plus' or 'possible early plus disease' or 'mild dilation, but not plus disease'. In these cases, do not record 'plus disease' as present. If the ophthalmologist records plus disease by quadrants, two or more quadrants are required to meet criteria for plus disease (i.e. only one quadrant of dilated/tortuous vessels is not sufficient.).

7. **Threshold (New Type 1 threshold per ETROP)**
The ophthalmologist who diagnoses threshold ROP needing surgery will normally state this prominently on the examination form. The criteria for the new threshold are any of the following four findings:

If in zone I: stage 3 ROP, even without plus disease
plus disease with any stage ROP

If in zone II: plus disease with stage 2 ROP
plus disease with stage 3 ROP

There may be times when disease is worse than this, but it should still be recorded as threshold. There will be some times when the judgment of the retinal surgeon and

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neonatologist will be not to administer treatment (laser or cryo), even when there is new threshold. Normally infants are then followed extremely closely (every few days repeat examinations).

8. **Surgery**
   For each examination date, record if surgery is performed on that day. (mostly will be no). If surgery was previously performed, but not on the day of that examination, record 0

9. **Post-surgical Retinal Detachment after surgery**
   This at first looks like a repeat of the question asking for stage of ROP, but it is not since it is intended to be used only after surgery has occurred.

10. Final Acute Status Lost to Follow-up at 55 weeks PMA
    Complete this question **only** for the final eye exam entered.

    Record 'N' if the last examination meets criteria for final acute status reached (see section 15.2 below).

    Record 'Y' if the final 'acute' ROP status is permanently missing because the infant is lost-to-follow up. For example, the last exam is not yet mature, or not yet in zone III for the second time in a row, or the baby still has ROP, but had not reached criteria for surgery. All attempts must have been made to capture this data from the follow up exams, and it is coded 'Y' as missing only when there was no final exam done (parents did not bring infant in).

    By the time an infant has reached 55 weeks PMA, the eye disease will have reached final status, whether we know about it from an examination or not. That is why we make this determination at this time. If it is later learned that examinations actually were done, the results can be entered on the form with a late correction/edit.

    Therefore, if you know the infant is less than 55 weeks PMA and has not had an exam that meets the final/acute criteria, you are still trying to get the family to bring the baby in for exams because it is clinically important and also will give you a primary study outcome. If it is now past 55 weeks, you may give up trying to get them to come in because it's too late to identify disease that could be treated, and the time for the clinical outcome for the study is also past. Late outcomes will be collected at the 18-22 month follow up examination.

    Potential merit of later exams: Most likely, they will reassure the infant that the eyes have healed. They may detect an important need for glasses at 6-9 months after birth. If the outcome is retinal detachments, the parents will learn the baby is not going to see and needs to be referred for early intervention. In either event, late exams that show retinal detachments will confirm that once upon a time, the baby did have bad ROP. Late exams that show good outcomes will NOT tell us if they once had ROP that has now regressed (healed).

    Note: even in these circumstances where we have given up, the infant will still be tracked down for the 18-22 month follow up visit. At that time they are asked if any eye surgery was done after discharge / status. If yes, what surgery. If it was for ROP,

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then that will become a final status revision. Also, even if no surgery was done, but the child has experienced vision loss *from ROP*, this would also be a final outcome.

Note that some infants have vision loss that is not from ROP. This is usually "cortical vision loss" and is from brain injury.

11. Final ROP Status determined at 18 Moth Follow Up
Complete this question **only** for the final eye exam entered.

Answer this question as 'N' if the final acute status was already determined before 55 weeks PMA. That is, "no, we did not determine the final outcome based on the 18-22 month exam."

Also, answer this question as 'N' if the final status was not determined by 55 weeks PMA, AND it was not determined at the 18-22 month visit either. This would happen if there were no 18-22 month examination. It would also happen if there were an 18-22 month examination, but the parents report no eye surgery and no other eye exams so we don't know what happened to the ROP.

You can record 'Y' for the final ROP status obtained during the 18-22 month follow up visit only if the parents are now reporting to you eye surgery for ROP that you had not learned about before, or they are telling you about eye exams that you have not learned about before (or else you would have recorded it before). If this is the case, reports from the exam(s) and/or surgery should be obtained to determine what has happened. These data will likely require ophthalmology input to determine if the primary ROP outcome was reached. Examples: A. ROP can be assumed (imputed) to have reached surgical criteria if the infant's subsequent surgery is vitrectomy for retinal detachment, or is an exam under anesthesia with a diagnosis of ROP stage 4A, 4B or stage 5 ROP, or retinal fold crossing the macula. B. ROP may not have met laser/CRYO criteria if the surgery was for strabismus (crossed eye), plugged tear duct, or only examination under anesthesia, for example to rule out glaucoma.

Acute/final Status

An eye is 'acute/final" when it reaches one of the following points in time:
These can be a good outcome (favorable) as the ROP heals (regresses), or it can be the primary outcome variable event (unfavorable).

Favorable

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5 retinal detachment stage 4b

Other

- Infant dies.

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Instructions for 18 Month Follow-Up Exam Questions Related to Vision (From the Follow-Up Manual of Operations)

Record separately for each eye, a-e; Record '1' Yes, if in the examiner's judgment the child has strabismus, nystagmus, or roving eye movements. Record '2' No, if the examiner's judgment the child does not have strabismus, nystagmus, or roving eye movements. Record '3' Suspect, if the findings are intermittent and not consistent for the eye in question. Record '4' if findings are untestable.

a. Strabismus (any kind):

Record Yes '1', is child has intermittent or persistent esotropia (in-turning) or exotropia (out-turning) resulting in ocular malalignment, esophoria or exophoria.

Assess the child's ability to move his eyes to the right, left, up, and down by moving a light from side to side, up and down in the midline, and diagonally across the bridge of the nose. The eyes should move in a smooth and unrestricted manner. Check for any of the following abnormal eye movements and record Yes '1'.

1. Esotropia or esophoria on the left: Left eye appears to deviate internally.
2. Esotropia or esophoria on the right: Right eye appears to deviate internally.
3. Alternating esotropia or esophoria: Child can fix with either eye, but the opposite eye deviates.
4. Exotropia or exophoria on the left: Left eye appears to deviate externally.
5. Exotropia or exophoria on the right: Right eye appears to deviate externally.
6. Alternating exotropia or exophoria: Child can fix with either eye but the opposite eye deviates.

b. Nystagmus

Persistent involuntary oscillation of eyes in any/ all fields of gaze

c. Roving Eye Movements

Record Yes '1' for Random eye movements - appears unable to fix/follow.

d. Tracks 180° (Record as 1, 2 or 4)

Have the child follow a bright toy or light across 180° of the field of vision. Record YES '1' if child is successful in following 180°, else record NO '2' or '4' if the child is untestable.

e. Vision:

Record separately for each eye.

The examiner should question the caretaker about the child's vision. If the child is prescribed glasses or contact lenses, the examiner should ask the caretaker how well the child sees with the glasses or contact lenses. If more than one applies, score the highest.

Record '1' if vision appears normal.

Record '2' if child wears or was prescribed corrective lenses.

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Record '3' if child has an other abnormality affecting that eye other than a condition requiring corrective lenses but the impairment is not severe enough for the child to be considered blind in that eye.

Record '4' if child is considered to be blind but has some functional vision. For example, a condition that requires the child to have an object held directly in front of his/her face in order to see it, would be considered blind with some functional vision. This is consistent with a refraction definition of < 20-200 (legally blind).

Record '5' if child has no useful vision in that eye. This is consistent with a refraction definition of < 20-200 (legally blind).

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The SUrfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient

	Examination Results								Examination Results							
	Left Eye								Right Eye							STATUS***	
Date of Exam	`Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage In any Zone	"Plus Disease"	Threshold (New Type 1)	Surgery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest zone	Highest+ Stage In any Zone	"Plus Disease"	Threshold (New Type 1)	Surgery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 weeks PMA	Final ROP Status determined at 18M Follow Up
1.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
2.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
3.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
4.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
5.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
6.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
7.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
8.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
9.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N
10.__/__/____	__	__	__	__	Y N	Y N	__	__	__	__	__	Y N	Y N	__	__	Y N	Y N

LOCATION:	1= Inpatient	2 = Outpatient	3= Transfer Hospital

*ZONE:	1= I	2 = II	3= III	4 = Mature	5= Status post laser/cryo	9=Unable to determine

+ STAGE:	0= No ROP	1= Stage 1	2=Stage 2	3= Stage 3	4= Stage 4a or 4b	5= Stage 5	6= Post laser/cryo (do not use stages)	9 = Old scars, but no active ROP

^ SURGERY:	0= No surgery this day	1= Laser	2= Cryotherapy	3= Both laser/cryo	4=Scleral buckle	5= Vitrectomy	6= Other

**RETINAL DETACHMENT:	0= None	3= Partial, not involving macula (stage 4a)	4 = Partial, does involve macula (stage 4b)	5 = Complete	9=View obscured, can't tell

****** only answer these questions for the last eye exam entered***

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This form should be completed for all children examined at the 18 + 4 month visit.

A. PHYSICAL EXAMINATION

1. Weight: ___ . ___ kg
2. Recumbent length: ___ . ___ cm
3. Occipital-frontal circumference: ___ . ___ cm

B. NEUROLOGIC EXAMINATION (performed by certified examiner)

1. Eye

	Right	Left
a. Strabismus (any kind)	____	____
b. Nystagmus	____	____
c. Roving Eye Movements	____	____

1 = Yes 2 = No 3 = Suspect 4 = Untestable

d. Tracks 180° (Record as 1, 2, or 4) ____ ____

1 = Yes 2 = No 4 = Untestable

	Right	Left
e. Vision:	____	____

1 = Normal
2 = Wears or was prescribed corrective lenses
3 = Other abnormality
4 = Blind some functional vision
5 = Blind no useful vision

2. Hearing

a. Was a Follow-up audiologic assessment completed since initial discharge to home? Y N

1) If NO, is consult pending for assessment? Y N

If YES, follow-up audiologic assessment completed, specify type of testing (2-4)

If the type of hearing exam is unknown **skip to question 4**

2) Visual Reinforcement Audiometry (VRA)? Y N

If Yes,

a. Right ___ b. Left ___ c. Sound field only___

Results: 1=Pass 2=Fail 3=Equivocal 4=Unknown

3) Auditory Brainstem Response (ABR)? Y N

If Yes,

a. Right ___ b. Left ___

1=Pass 3=Equivocal
2=Fail 4=Unknown

4) Unknown type of hearing test? Y N

If Yes,

a. Right ___ b. Left ___

1=Pass 3=Equivocal
2=Fail 4=Unknown

b. Hearing impaired (based on observation +/- history)? ____

1 = No apparent functional impairment **+/- amplification**
2 = Impairment **+/- amplification**

Note: If hearing is impaired and baby is enrolled in the Phototherapy Trial, complete the NF14 (18 Mo. Hearing Assessment Form).

1) Hearing aid requirement: ____

0 = None 1 = Right only 2 = Left only 3 = Both

3. Oral motor skills

a. Swallowing ____

1 = Normal 2 = Abnormal 3 = Tube fed

For questions b-f indicate yes or no for all

b. Dysphagia (difficulty in swallowing) Y N

c. Documented aspiration Y N

d. Abnormal voice (soft or hoarse voice) Y N

e. Drooling Y N

f. Nothing by mouth Y N

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4. Nature of motor involvement with child in any comfortable position:

a. Observed abnormal movements? Y N

If Yes, abnormal,

1) Short –jerky Y N

2) Slow, writhing? Y N

3) Tremor Y N

b. Passive muscle tone: (use codes below for question 4.b. 1-3)

1 = Normal	4 = Suspect Decreased
2 = Suspect Increased	5 = Definite Decreased
3 = Definite Increased	6 = Varying tone

1) Neck and Trunk ___

	Right	Left
2) Upper extremity muscle tone:	___	___
3) Lower extremity muscle tone:		
a. Hip and knees	___	___
b. Ankles	___	___

5. Is there scissoring of the legs on vertical suspension? Y N

6. Gross Motor Function Level: ___
(Use work sheet (NF05A) to determine level)

1 = Normal	4 = Level 2	7 = Level 5
2 = Possible Level 1	5 = Level 3	
3 = Level 1	6 = Level 4	

7. Hand preference ___

1 = None	3 = Exaggerated Left
2 = Exaggerated Right	

C. REFLEXES / MOTOR SKILLS / DIAGNOSES

1. Protective reactions (anterior, lateral and parachute) ___

1 = Symmetric 2 = Asymmetric 3 = Not present

2. Limb movements

1 = Symmetrical 2 = More on right 3 = More on left

a. Upper limbs ___

b. Lower limbs ___

For questions 3 – 5 use the following codes
1 = Normal (1 to 3+) 2 = Absent (0) 3 = Hyperactive (4 +)

	Right	Left
3. Deep tendon reflexes – upper extremities	___	___
4. Deep tendon reflexes – knees	___	___
5. Deep tendon reflexes – ankles	___	___
6. Ankle clonus	___	___

1 = None (≤ 4 beats)
2 = Present (> 4 beats)
3 = Sustained

7. Plantar reflexes ___ ___

1 = Flexor plantar response	3 = Spontaneous extension ± fanning
2 = Extensor plantar response	4 = Inconsistent results

8. Functional gross motor skills

a. Axis-head and neck: ___

1 = Normal head control
2 = Abnormal, but can hold head up for extended period (≥ 5 min.)
3 = Poor head control but can hold head up for short period
4 = No obvious head control

b. Axis-trunk: ___

1 = No apparent problem
2 = Can sit unsupported but less secure and stable than normal child of same age
3 = Cannot be left in sitting position unless self-supported
4 = Severe impairment: Difficult to place or maintain in sitting position

c. Lower limb function-gait: ___

1 = No significant problem with gait; walks fluently
2 = Gait functional but not fluent, no device required
3 = Gait functional, non-fluent and requires device
4 = No independent walking

d. Upper limb function: ___

1 = No apparent problem with bimanual tasks
2 = Some difficulty using both hands together
3 = No functional bimanual task

e. Hand function: 1) Right 2) Left ___ ___

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1 = Fine pincer grasp
2 = Finger-Thumb grasp
3 = More than one finger-thumb (rake) grasp
4 =Tries but unable to grasp
5 =Does not attempt to grasp
6 = Refusal
7 = Cannot assess

9. Diagnoses: Neurologic/Motor disorder

a. Normal?	Y	N
b. If NEURO ABNORMAL (OTHER THAN CEREBRAL PALSY),		
1) Generalized hypotonia?	Y	N
2) Hypertonia?	Y	N
3) Other; if yes, describe:_____	Y	N
c. If NEURO ABNORMAL (CEREBRAL PALSY),		
1) Spastic diplegia?	Y	N
2) Spastic hemiplegia - right?	Y	N
3) Spastic hemiplegia - left?	Y	N
4) Spastic quadriplegia?	Y	N
5) Spastic triplegia?	Y	N
6) Athetosis/dystonia with varying tone?	Y	N
7) Hypotonic with + ataxia?	Y	N
8) Spastic monoplegia?	Y	N
9) Mixed cerebral palsy?	Y	N
10) Cerebral palsy, otherwise unclassified. If yes describe:_____	Y	N
10. Does this child have cerebral palsy?	Y	N

If YES, classification of cerebral palsy: ___

1 = Mild 2 = Moderate 3 = Severe

11. Congenital and/or acquired abnormalities affecting neurodevelopmental assessment?	Y	N

If YES, specify: _____

D. FORM COMPLETION

1. Where was exam completed: ___

1 = Clinic 2 = Home 3 = Other Clinic 4 = Hospital
9 = Other (specify): _____

2. Quality of the exam? ___

1 = Good 2 = Fair 3 = Poor

If Fair (2) or Poor (3), factors affecting the exams? ___

Codes for reasons not successfully tested
1 = Illness
2 = Language other than English and interpreter not available
3 = Behavioral problems
4 = Severely developmentally delayed plus may have sensory impairment (Bayley score of 49)
5 = Sensory impairment - appears mild or moderately delayed for age
6 = Sensory impairment - but appears to be within normal limits for age
9 = Other: (Specify)_____

3. Date exam completed: __/__/__/__ __ __ __
Month Day Year

4. Initials of person administering Infant examination: ___ ___ ___

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From: Finer, Neil
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade; Wally Carlo
Subject: Re: Paper
Date: Wednesday, October 21, 2009 11:29:07 AM
Attachments: SUPPORT CPAP vs Surf Oct 21 09.doc.rtf

Hi Marie
I had gotten these before. Can you please insert the relative risks as Abhik has asked for. Once we have final data lock, you will need to check that all the values and P values etc and stats are corrected.
Please see my comments to you in yellow. We need to correct the study number to 1317 and correct each group size.
I have not attached the Tables as you have them and I made no changes to them.
Thanks Marie
I want to get this paper out to the committee and then ready for submission
Neil

On 10/21/09 7:17 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

Comments from Ken. Not sure if he sent them to anyone but me.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Poole, W. Kenneth
Sent: Tuesday, October 20, 2009 12:29 PM
To: Gantz, Marie
Subject: FW: Paper

Correction.

From: Poole, W. Kenneth
Sent: Sunday, October 18, 2009 5:45 PM
To: Gantz, Marie
Subject: Paper

Marie,
A few comments on the paper. (red). I assume we will also have a table on the primary outcomes.

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of consenting parents of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP or surfactant; those randomized to CPAP had CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings and infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1317 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group (all p<0.001), and 67% of the CPAP infants received surfactant at any time during their hospitalization,. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p < 0.05$, Marie can you please provide the RR and CI when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, p=0.03). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015) and fewer required post natal steroids for BPD, (p<.0004). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants requiring intubation during their nursery course, (p<0.001). There were no differences between the groups for air leaks including pneumothoraces.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with

Comment [AD1]: I would provide the relative risk and 95% CI instead of, or in addition to the p value. Same goes for other CPAP vs surfactant outcome comparisons, both here and in the main text.

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the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

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The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses[46], and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

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In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were

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randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

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These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine, with sufficient power, an interaction effect between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

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The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

Results:

There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. Marie can you correct these – we had one additional child and I do not know which arm that infant was in – the Tables need correcting for the actual number as well – they all total 1316 – and we have 1317 There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not significant.

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In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified Marie we need the RR etc as Abhik has asked for)). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata, Table 4. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, p=0.27. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (40% vs 41%, p=0.96), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=0.32).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.01). There were no differences between the groups in air leaks in the first 14 days, air leaks during the hospital

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stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, p=.0004).

Strata Results: 24 – 25 weeks Gestation

Comment [AD2]: Do we need to preface some justification for looking within strata?

There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, p=0.~~03~~028. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, $p<0.01$, lesser days of mechanical ventilation, 10.7 vs 14.2, $p<0.01$, and less postnatal steroids for BPD, 3% vs 8%, $p<0.01$.

Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[1414] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.**[8] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. We also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a

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complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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From: Cunningham, Meg
To: Kimberley A Fisher
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Irene, Amanda
Subject: RE: Images for SUPPORT Secondary
Date: Wednesday, October 21, 2009 9:33:05 AM

Kim,

You can still send us that HUS. Any chance you can overnight it so it gets to me tomorrow? Also, please make sure the MRI01 form gets entered.

It should be sent to:

Amanda Irene
RTI International
6110 Executive Boulevard, Suite 902
Rockville, MD 20852-3907
Phone: 301-230-4640

Thanks!
Meg

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Wednesday, October 21, 2009 8:51 AM
To: Cunningham, Meg
Subject: RE: Images for SUPPORT Secondary

Meg
I found one child that was consented that an early US but then died at less than 2 weeks of age -

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Cunningham, Meg" <mcunningham@rti.org>

10/20/2009 03:11 PM

To "Kimberley A Fisher" <kimberley.fisher@duke.edu>
cc <gloria.siaw@duke.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject RE: Images for SUPPORT Secondary

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Thanks for the clarification Kim.

Are you aware of any other subjects who were enrolled but do NOT have an MRI01 form? I want to make sure I have all images no later than Thursday, as the last reading in Detroit begins this weekend.

Thanks for all the help,
Meg

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Tuesday, October 20, 2009 1:53 PM
To: Cunningham, Meg
Cc: gloria.siaw@duke.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Images for SUPPORT Secondary

Meg
We are so sorry for the confusion. You are correct that subjects (b) (6) and (b) (6) are NOT consented for the MRI secondary study. Please destroy the discs that were sent.

For subject (b) (6) this subject was consented for the MRI study and I have entered the MRI01 into the DMS and transmitted it as well. This subject had 2 head US that were both normal. The second was not done in window and there was no MRI done.

Thank you for your continued oversight and work on this study!

Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b) (6)
Email: kimberley.fisher@duke.edu

"Cunningham, Meg" <mcunningham@rti.org>

10/20/2009 12:24 PM

To <gloria.siaw@duke.edu>, <Kimberley.fisher@duke.edu>
cc "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject Images for SUPPORT Secondary

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Gloria and Kim,

In a recent shipment of images you sent me images for:

(b) (6)
[redacted]
[redacted]

According to the data these kids are NOT enrolled in the MRI secondary. Both (b) (6) and (b) (6) do NOT have MRI01 forms. (b) (6) does have an MRI01 form, but it is indicated that this kid was NOT enrolled because you were not able to contact the family.

Are these kids enrolled into the study? If so, the MRI01 forms need to be entered and corrected. If they are NOT enrolled in the study, please let me know. I am attending the last reading later this week and do not want to read any images that I don't have to.

Please get back to me as soon as you can.
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org

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From: Gantz, Marie
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik
Subject: RE: SUPPORT Studies
Date: Tuesday, October 20, 2009 3:30:18 PM

Will do.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 20, 2009 3:29 PM
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: Re: SUPPORT Studies

Thanks Marie
For now we will report BPD using oxygen to include only infants on oxygen.
Later in a subsequent paper we can use the CPAP/Vent +RA infants. For this
the queries will be useful as I have already seen some for which the infant
was Post-op for eye surgery - this would not be BPD
The only possible adjucation for BPD would be whether others want to look at
the physiologic definition infants - there the results were not close to significant so I don't see how that would change things but lets get all the
final queries. Once you have those lets finalize the BPD numbers and stats.
Whenever you can finalize the Consent paper please send to Rose as she needs
to get Approval to submit
Thanks
Neil

On 10/20/09 12:18 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

> Wade's paper does need input from me - there were several edits done in
> response to queries I sent out that have not been incorporated. The
> changes will be small. I apologize for the delay in getting those
> results out - all my time has been taken up by the SUPPORT edits and
> queries.
>

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> Sites have been working on the SUPPORT queries and I will know where we
> stand after the data the centers will transmit today have been processed
> (which won't take place until tomorrow). I should be able to send you
> results for the SC meeting. Will there be adjudication for BPD, or only
> for ROP? I have asked centers to reply with reasons that infants are on
> RA by vent/CPAP, and for some of them, the reason has been "infant has
> BPD." I'm wondering if those cases need to be looked at. I will send you
> a list of those cases and the responses when I have them all.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Tuesday, October 20, 2009 2:51 PM
> To: 'Finer, Neil'; Gantz, Marie; Das, Abhik
> Cc: Rich, Wade; Zaterka-Baxter, Kristin
> Subject: RE: SUPPORT Studies
>
> Neil
> We need Wade's paper for NICHD clearance.
>
> I sent the last set of queries out early Saturday morning to the sites.
> Three has been a lot of email traffic with queries being answered. Kris
> also sent queries for protocol violations yesterday.
> Plan is for data lock after DMS transmission today. I am working on a
> ROP adjudication, but it appears that we have death/ROP outcome on > 90%
> of the infants!!
>
> Rose
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, October 20, 2009 2:49 PM
> To: Gantz, Marie; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Rich, Wade
> Subject: SUPPORT Studies
>
> Hi Marie
> A couple of queries
> Where are we with Wades consent paper? - Does it require more input from
> you? I think that this paper is ready for submission if you are done
> with it.

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> What is the status of the SUPPORT data regarding the final queries and
> edits for the stats?
> Will you be able to put the final values and stats in the paper in
time
> to send the Surf-CPAP paper out for the Subcommittee meeting. I
realize
> that ROP data may be more complex, but I would like an update so that
I
> can prepare for the meeting.
> Thanks
> Neil

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Studies
Date: Tuesday, October 20, 2009 2:52:30 PM

Rose,
I am waiting on new calculations from marie.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 20, 2009 2:51 PM
To: Finer, Neil; Gantz, Marie; Abhik Das
Cc: Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Studies

Neil
We need Wade's paper for NICHD clearance.

I sent the last set of queries out early Saturday morning to the sites. Three has been a lot of email traffic with queries being answered. Kris also sent queries for protocol violations yesterday.
Plan is for data lock after DMS transmission today. I am working on a ROP adjudication, but it appears that we have death/ROP outcome on > 90% of the infants!!

Rose

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 20, 2009 2:49 PM
To: Gantz, Marie; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: SUPPORT Studies

Hi Marie
A couple of queries
Where are we with Wades consent paper? - Does it require more input from you? I think that this paper is ready for submission if you are done with it.
What is the status of the SUPPORT data regarding the final queries and edits for the stats?
Will you be able to put the final values and stats in the paper in time to send the Surf-CPAP paper out for the Subcommittee meeting. I realize that ROP data may be more complex, but I would like an update so that I can prepare for the meeting.
Thanks
Neil

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From: Susan Hintz
To: Newman, Jamie
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Please review: technical memos-SUPPORT Neuroimaging/Neurodev Outcomes Secondaries
Date: Tuesday, October 20, 2009 2:21:46 PM

Hi Jamie and Rose

Thanks - these look great.

It may be helpful to send an email out again to the site - or even add the information to the technical memo - about when the tracking form is "delinquent". I believe the coordinators are very concerned on that point.

Thanks again for all your hard work!

Susan

> Rose, Susan, and Kristi,
>
> Attached is the technical memo I have drafted that spells out tracking for the SUPPORT MRI School Age Follow-up. I have placed the information that I have been emailing in the attached technical memo. Because the Object Permanence Ancillary Form (MRI09A) was released at about the same time, questions about that secondary go hand in hand with the SUPPORT MRI School Age Follow-up tracking at 3-4 years. So, I have also drafted a memo that spells out exactly which pts should have the MRI09A form completed. Again, this memo includes information that I have been sending in emails.
>
> I'd like to distribute these memos at the same time and will post them to the website where their respective forms and protocols are located. In the meantime, please let me know if you have any changes.
>
> Thanks, Jamie
>
> ---
>
> **From:** Newman, Jamie [mailto:newman@rti.org]
> **Sent:** Thursday, October 01, 2009 9:30 AM
> **To:** Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]
> **Cc:** Johnson, Karen; Bell, Edward; Zaterka-Baxter, Kristin
> **Subject:** RE: school age follow up - information on tracking
>
> Below are the emails that I have recently sent concerning tracking for the SUPPORT MRI School Age Follow-up. I will draft a technical memo outlining this information (to be posted

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on the website) to avoid further confusion. Thanks for letting us know that it is a point of confusion.

Jamie

Content-Type: application/msword;
name="Technical Memo_Obj_Permanence_Ancillary.doc"
Content-Description: Technical Memo_Obj_Permanence_Ancillary.doc
Content-Disposition: attachment;
filename="Technical Memo_Obj_Permanence_Ancillary.doc"

Attachment converted: Macintosh HD:Technical Memo_Obj_P#6C2FA2.doc (WDBN/«IC») (006C2FA2)
Content-Type: application/msword;
name="Technical Memo_Tracking_SUPPORT_MRI School age FU.doc"
Content-Description: Technical Memo_Tracking_SUPPORT_MRI School age FU.doc
Content-Disposition: attachment;
filename="Technical Memo_Tracking_SUPPORT_MRI School age FU.doc"

Attachment converted: Macintosh HD:Technical Memo_Track#6C2FA3.doc (WDBN/«IC») (006C2FA3)

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From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ATS 2010
Date: Tuesday, October 20, 2009 2:13:23 PM

Other suggestions: john kinsella (Colorado), alan jobe (was he part of SUPPORT?), rose higgins (u. md), roberta ballard (though I am not sure she is coming),
Preferences for who to start with?
Carol

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 20, 2009 2:09 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: ATS 2010

They would be fine – if you want an "Oxygen toxicity" person, you may want Eduardo Bancalari. Also, Rochester recruited 8 infants into SUPPORT. Bancalari is from Miami and I believe they recruited slightly less than 20. I am fine with your suggestions

Rose

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Tuesday, October 20, 2009 1:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ATS 2010

Dale Phelps has declined the invitation (see below). Perhaps Sesh Cole/Aaron Hamvas, Larry Nogee, who I think typically attend ATS could be discussant??--Carol

Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 20, 2009 11:03 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: ATS 2010

Thank you for the kind invitation Carol,
I must decline for two reasons. The first is that University of Rochester was a participating center in the SUPPORT trial to be discussed, and second that I do not attend the ATS meeting.
Dale

Dale Phelps, MD
Professor of Pediatrics
University of Rochester

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From: Blaisdell, Carol (NIH/NHLBI) [E] [mailto:blaisdellcj@nhlbi.nih.gov]
Sent: Tuesday, October 20, 2009 6:57 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ATS 2010

Dear Dr. Phelps,

The Division of Lung Diseases-NHLBI and NICHD are holding a noon session at ATS in New Orleans, Sunday, May 16th on Outcomes from the NHLBI-NICHD SUPPORT Trial: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight (ELBW) Infants. Dr. Neil Finer and Carlo Waldemor will be presenters, and Rose Higgins (NICHD Neonet) and I would like to invite you to be a discussant of the trial results.

Will you be attending ATS, and will you be interested in being a discussant for the SUPPORT session on May 16, 2010?

Thanks for your consideration, Carol

Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call
Date: Tuesday, October 20, 2009 2:11:18 PM

I have no information because I don't know any of them. David did oint out one woman from Duke.

I think it is important, however, to have non-Duke people.

If any of the "old favorites" from non-network centers could be asked, they would be very valuable.
Earl palmer, oregon
Graham Quinn, CHOP
Michael Chiang, Columbia
Michael Repka, pvt practice, MD
William Good, San Francisco
? Bob Gordon, Tulane

I can keep looking after I get home tonight.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Phelps, Dale
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tue Oct 20 12:55:22 2009
Subject: RE: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dale-
I am fine with using any of the ones that David suggests – if we use 3 total, who are choices along with David?

Thanks
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, October 12, 2009 3:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: FW: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Hi Rose,
I have concerns.

You only have one ophthalmologist. David Wallace can not be the only person in the group that has the clinical experience to make these judgements.
A phone call is a very inefficient use of time for these judgments . Especially with that many people, I don't think it will work well.
But maybe this is just a planning session?

David has identified 5 other ophthalmologists form our NRN centers that he thinks would be good. I will include his list. I have a partial draft letter, not sent, for them [attached] because I was waiting to talk to Abhik and Rose and Kris about how we would do this. Maybe you have decided already ???
Sharon Freedman here at Duke is excellent, and she knows plus disease. Which centers are in

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the Network?
David

Dale, From the list, I recommend 4 others (should make 6 if all agree):
Hutchinson
Hoffman
Neely
Yang
David

The Adjudication committee can not make a judgment about the primary outcome.
We have not established what the process will be, and that should be done before cases are examined.
I can help you a lot with how to present the data to the adjudication committee so that they can most efficiently absorb it.

Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, October 12, 2009 11:48 AM
To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dear all,

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
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(fax) 919.485.7762
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RTP, NC 27709 USA

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From:	Newman, Jamie
To:	Higgins, Rosemary (NIH/NICHD) [E]; srhintz@stanford.edu; kwatterberg@salud.unm.edu
Cc:	Conra Lacy
Subject:	Please review: technical memos-SUPPORT Neuroimaging/Neurodev Outcomes Secondaries
Date:	Tuesday, October 20, 2009 1:18:19 PM
Attachments:	Technical Memo_Obj_Permanence_Ancillary.doc Technical Memo_Tracking_SUPPORT_MRI School age FU.doc

Rose, Susan, and Kristi,
Attached is the technical memo I have drafted that spells out tracking for the SUPPORT MRI School Age Follow-up. I have placed the information that I have been emailing in the attached technical memo. Because the Object Permanence Ancillary Form (MRI09A) was released at about the same time, questions about that secondary go hand in hand with the SUPPORT MRI School Age Follow-up tracking at 3-4 years. So, I have also drafted a memo that spells out exactly which pts should have the MRI09A form completed. Again, this memo includes information that I have been sending in emails.

I'd like to distribute these memos at the same time and will post them to the website where their respective forms and protocols are located. In the meantime, please let me know if you have any changes.

Thanks, Jamie

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Thursday, October 01, 2009 9:30 AM
To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Johnson, Karen; Bell, Edward; Zaterka-Baxter, Kristin
Subject: RE: school age follow up - information on tracking

Below are the emails that I have recently sent concerning tracking for the SUPPORT MRI School Age Follow-up. I will draft a technical memo outlining this information (to be posted on the website) to avoid further confusion. Thanks for letting us know that it is a point of confusion.
Jamie

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RTI INTERNATIONAL | **Memorandum**

Date: October 20, 2009

To: NICU PIs, Coordinators, Follow Up PIs, Follow-up Coordinators participating in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary study

From: Data Coordinating Center

Re: Object Permanence Ancillary Form (MRI09A)

The MRI09A Form (version dated 1/6/09 distributed January 12, 2009) is the Object Permanence Ancillary Form. It should be completed only for babies enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary study that are seen at 18 months and have a Bayley III exam.

The MRI09A form is used to record three additional items from the Bayley III exam administered at the 18 month follow-up visit. These three additional Bayley III items (40, 45, 50) will be recorded to assess early working memory by evaluating object permanence. As was stated in the protocol, patients not yet seen for the 18 month follow-up visit will have these three additional items recorded prospectively. There were approximately 70 patients from this study who had already been seen for the 18 month follow-up visit when the MRI09A form was released. The three items for these patients will be collected by NRN Center staff from the Bayley III score sheets, if retained.

The MRI09A form is located on the NRN website:
Protocols – SUPPORT – Secondary Studies – Object Permanence Ancillary – Forms – MRI09A

RTI has been posting Object Permanence Ancillary Pending Reports since March 2009 on the private gateway of the NRN website with the other site-specific reports under: Administration – Site Reports – [Click on Your Center] – Object Permanence Ancillary (MRI09A) Pending Report.

Patients are included on this pending report if they participated in the Neuroimaging and Neurodevelopmental Secondary to SUPPORT and have already been followed at 18 months (and had a Bayley exam). Patients with windows yet to open are also included in this report. Once the MRI09A form has been keyed, patients will no longer appear on the pending report.

Please submit any questions to Jamie Newman at newman@rti.org.

Note: The Object Permanence Ancillary Study protocol and MRI09A form are posted to the private gateway of the NRN website under this location:
Protocols – SUPPORT – Secondary Studies – Object Permanence Ancillary - Protocol
Protocols – SUPPORT – Secondary Studies – Object Permanence Ancillary - Forms – MRI09A

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RTI INTERNATIONAL | **Memorandum**

Date: October 20, 2009

To: NICU PIs, Coordinators, Follow Up PIs, Follow-up Coordinators Center participating in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary study

From: Data Coordinating Center

Re: Tracking for SUPPORT MRI School Age Follow-up Patients

The SEF01 Form (version dated 1/7/09 distributed January 8, 2009) is the 3-4 Year Status Form for the SUPPORT MRI School Age Follow-up Study. This form should be completed only for patients enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes study with a successful MRI who were discharged from the hospital alive.

The SEF01 form is located on the NRN website:
Protocols – SUPPORT – Secondary Studies – MRI School Age Follow-up - Forms – SEF01

Tracking tools were added to Centers' Network computers in early January 2009 which list which patients should have the SEF01 form completed. Once coordinators have contacted the SUPPORT families involved in the Neuroimaging and Neurodevelopmental Outcomes study at 3-4 years of age, they are asked to key the SEF01 Form so that the 3-4 year status will show up in the tracking reports. Following are instructions for using these tracking tools that were distributed when the reports were added to the Network computers:

Upon opening the Support DMS, select the "Reports" button. At the bottom of the report list you have the option to select either "6.5-7.5 Yr Follow-up Tracking List" or "6.5 to 7.5 Yr Follow-up Patient Contacts".

6.5-7.5 Yr Follow-up Tracking List:
This is a listing of all patients randomized into Support with a successful MRI. It provides the user with necessary 6.5 to 7.5 year follow-up dates and lists the patients' status at various protocol data points. There are three display options for the listing, these are as follows.

View Report: The report will open in MS Access so the user can view the complete listing of patients randomized into Support with an MRI.

Print Report: The report will print to the user's default printer.

Export to Word or Excel: A window will appear asking the user if they want to export the listing. Upon clicking "Yes", the user will be asked to provide the directory path where they want the document to be saved (the default location is c:\network\nicu\followup - this can be changed to any valid directory on the computer). Next the file name will be requested (the default name is Supp6to7_YYYYMMDD.xls – 'YYYY' being the four digit year, 'MM' being a two digit month and 'DD' being a two digit day. This can be changed as well). Click OK and the spreadsheet will be saved. The Excel document does NOT automatically open up after it is exported.

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6.5 to 7.5 Yr Follow-up Patient Contacts:

This is a follow-up tool which is a full-page document for each patient. It provides the user with the patient ID, needed dates and space to hand write the patient's contact information. There are two display options for this tool, these are as follows.

View Report or Print Report: A window will open listing all the randomized Support patients with an MRI (user must scroll down to see all the IDs). The user will click on the check box next to the patient ID for which they want the tool created. They then will click on the "View Tool" or "Print Tool" button. "View Tool" opens the document for viewing. The "Print Tool" prints the document directly on the user's default printer. To go back to the previous screen the user will click "Return".

Export to Word or Excel: The user will click on the check box next to the patient ID for which they want to export a document to Word. They will then click on the "Export to Word" button. A window will appear asking the user if they want to export the listing. Upon clicking "Yes", the user will be asked to provide the directory path where they want the document to be saved (the default location is c:\network\nicu\followup - this can be changed to any valid directory on the computer). Next the file name will be requested (the default name is ContactList_YYYYMMDD.rtf – 'YYYY' being the four digit year, 'MM' being a two digit month and 'DD' being a two digit day. This can be changed as well). Click OK and the document will be saved. The Word document does NOT automatically open up after it is exported. To go back to the previous screen the user will click "Return".

Please submit any questions to Jamie Newman at newman@rti.org.

Note: The SUPPORT MRI School Age Study protocol and SEF01 form are posted to the private website under this location:

Protocols – SUPPORT – Secondary Studies – MRI School Age Follow-up - Protocol
Protocols – SUPPORT – Secondary Studies – MRI School Age Follow-up - Forms – SEF01

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From: Gantz, Marie
To: Zaterka-Baxter, Kristin; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: adjudication
Date: Tuesday, October 20, 2009 12:41:28 PM

Hi all,

Please note that what I just sent out was a sample of 3 infants so that Dale could look at the information being included in the report and make any changes that are necessary. I will send out the actual report for the adjudication committee as soon as data transmitted to RTI today have been processed.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Zaterka-Baxter, Kristin
Sent: Tuesday, October 20, 2009 12:38 PM
To: Gantz, Marie; 'Phelps, Dale'; 'higginsr@mail.nih.gov'; Das, Abhik
Subject: RE: adjudication

Hi,
Please let me know when I can send this on to Dr. Wallace.
Thanks!
Kris

From: Gantz, Marie
Sent: Tuesday, October 20, 2009 12:33 PM
To: 'Phelps, Dale'; higginsr@mail.nih.gov; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: adjudication

Dale,

Please let me know if this report format will suit your purposes for the adjudication.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 14, 2009 2:06 PM
To: higginsr@mail.nih.gov; Das, Abhik; Zaterka-Baxter, Kristin; Gantz, Marie
Subject: Re: adjudication

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I should be able to help set up that page. Please send me a sample of 3 kids. I can look at it and spot other information that might help.

You should also add the 18-20 month visual outcomes.

Dale

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; Phelps, Dale
Sent: Wed Oct 14 09:13:53 2009
Subject: FW: adjudication

We will need an adjudication. We should have 3 ophthalmologists who are unaware of any study results look at the exams with indeterminate outcomes. We will need a table for each child constructed as follows:

Post menstrual age at exam (weeks)	Chronologic age at exam (in weeks)	Next several columns – data from SUPP10 for each exam				

For each infant, we will need birth weight and gestational age at birth – data must be de-identified (no dates).

I will look over the list that David Wallace sent and select folks for you to contact by the end of the day
Dale – do I have the necessary items in the table?
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 13, 2009 5:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: adjudication

If this were Inositol, I would yes absolutely yes.

Because SUPPORT is more complex I'm not so sure (with the 2x2 design, four outcome cells for analyses, 2 different primary outcomes).
However, I would favor having it in there. It relieves some uncertainties.

Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 1:50 PM
To: Phelps, Dale; Abhik Das

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Cc: Zaterka-Baxter, Kristin
Subject: RE: adjudication

Dale
Does this need to appear in the primary paper??
Thanks
rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 13, 2009 4:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Cc: Zaterka-Baxter, Kristin
Subject: RE: adjudication

I think it is worth the effort to do the adjudication. The results will be:
some who did have an adverse primary study outcome
many who had a good long term outcome, but we'll never know if they actually met criteria and resolved spontaneously
several that we'll be able to say almost certainly never met the criteria for the primary outcome data.

Given those three categories, it is very helpful to look at the primary outcome data and ask:
IF WE ASSUME
the probably bad were bad (first category)
and the probably good were good (last category)
and list a missing the middle category..... what does that do to the analysis?
the usual conclusion is 'no effect on conclusions'
this is very reassuring
it is reasonably conservative ... but ask Das and Wallace

IF further want to add in the 'middle category' in some fashion, I'd say worst case scenario, assume half good and half not... what does that do?

....
So if I'm a reviewer, I want to know that you examined the impact of these unknowns on your primary outcome. I don't want you to change your primary outcome, but I want you to do the work to tell me what the impact of those missed kids could have been. Would they have potentially changed your conclusions?
Usually when you do this you find that the answer is "No". (when there is pretty good follow up)

when the answer is squishy, it is usually because the follow up rates are quite bit lower, like 70-80%

Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 12:19 PM
To: Phelps, Dale
Cc: 'Zaterka-Baxter, Kristin'; 'Das, Abhik'
Subject: adjudication

Dale
I have a practical pragmatic question –if the likely results for the adjudication are "unable to determine," is there a reason to expend the effort?

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Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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National Institutesof Health
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higginsr@mail.nih.gov

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From: Gantz, Marie
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: adjudication
Date: Tuesday, October 20, 2009 12:33:31 PM
Attachments: ROP adjudication sample data 20OCT09.rtf

Dale,

Please let me know if this report format will suit your purposes for the adjudication.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
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Rosemary D. Higgins, MD
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SAMPLE DATA FOR ROP ADJUDICATION

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)
1	1025	27	4

Infant number	SUPP10 exam: Eye	SUPP10 exam: Number	SUPP10 exam: Location	SUPP10 exam: PMA (weeks)	SUPP10 exam: Chronological age (weeks)	SUPP10 exam: Lowest zone of any vessels	SUPP10 exam: Highest stage in lowest zone	SUPP10 exam: Highest stage in any zone	SUPP10 exam: Surgery	SUPP10 exam: Post-surgical retinal detachment
1	Left	1	1	32.57	5	2=II	0=No ROP	0=No ROP	0=No surgery this day	.
		2	1	34.43	6.86	2=II	0=No ROP	0=No ROP	0=No surgery this day	.
		3	1	64.29	36.71	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
	Right	1	1	32.57	5	2=II	0=No ROP	0=No ROP	0=No surgery this day	.
		2	1	34.43	6.86	2=II	0=No ROP	0=No ROP	0=No surgery this day	.
		3	1	64.29	36.71	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None

Infant number	FU exam: Eye	FU exam: Strabismus	FU exam: Nystagmus	FU exam: Roving eye movements	FU exam: Tracks 180 degrees	FU exam: Vision
1	Left	2=No	2=No	2=No	1=Yes	1=Normal
	Right	2=No	2=No	2=No	1=Yes	1=Normal

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)
2	800	24	6

Infant number	SUPP10 exam: Eye	SUPP10 exam: Number	SUPP10 exam: Location	SUPP10 exam: PMA (weeks)	SUPP10 exam: Chronological age (weeks)	SUPP10 exam: Lowest zone of any vessels	SUPP10 exam: Highest stage in lowest zone	SUPP10 exam: Highest stage in any zone	SUPP10 exam: Surgery	SUPP10 exam: Post-surgical retinal detachment
2	Left	1	1	31	6.14	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		2	1	32	7.14	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		3	1	35	10.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		4	1	37	12.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		5	1	40	15.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		6	1	41.57	16.71	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		7	1	44.57	19.71	3=III	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		8	.	.	.	.	.	.	.	.
	Right	1	1	31	6.14	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		2	1	32	7.14	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		3	1	35	10.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		4	1	37	12.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None

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SAMPLE DATA FOR ROP ADJUDICATION

Infant number	SUPP10 exam: Eye	SUPP10 exam: Number	SUPP10 exam: Location	SUPP10 exam: PMA (weeks)	SUPP10 exam: Chronological age (weeks)	SUPP10 exam: Lowest zone of any vessels	SUPP10 exam: Highest stage in lowest zone	SUPP10 exam: Highest stage in any zone	SUPP10 exam: Surgery	SUPP10 exam: Post-surgical retinal detachment
		5	1	40	15.14	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		6	1	41.57	16.71	2=II	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		7	1	44.57	19.71	3=III	2=Stage 2	2=Stage 2	0=No surgery this day	0=None
		8	.	.	.	.	.	.	.	.

Infant number	FU exam: Eye	FU exam: Strabismus	FU exam: Nystagmus	FU exam: Roving eye movements	FU exam: Tracks 180 degrees	FU exam: Vision
2	Left	2=No	2=No	2=No	1=Yes	1=Normal
	Right	2=No	2=No	2=No	1=Yes	1=Normal

Infant	Birth Weight (grams)	Gestational Age (weeks)	Gestational Age (days)
3	980	25	5

Infant number	SUPP10 exam: Eye	SUPP10 exam: Number	SUPP10 exam: Location	SUPP10 exam: PMA (weeks)	SUPP10 exam: Chronological age (weeks)	SUPP10 exam: Lowest zone of any vessels	SUPP10 exam: Highest stage in lowest zone	SUPP10 exam: Highest stage in any zone	SUPP10 exam: Surgery	SUPP10 exam: Post-surgical retinal detachment
3	Left	1	1	31.43	5.71	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		2	1	33.29	7.57	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		3	1	36.43	10.71	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		4	3	38.43	12.71	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		5	2	55.71	30	3=III	0=No ROP	0=No ROP	0=No surgery this day	0=None
	Right	1	1	31.43	5.71	2=II	0=No ROP	0=No ROP	0=No surgery this day	0=None
		2	1	33.29	7.57	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		3	1	36.43	10.71	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		4	3	38.43	12.71	2=II	1=Stage 1	1=Stage 1	0=No surgery this day	0=None
		5	2	55.71	30	3=III	0=No ROP	0=No ROP	0=No surgery this day	0=None

Infant number	FU exam: Eye	FU exam: Strabismus	FU exam: Nystagmus	FU exam: Roving eye movements	FU exam: Tracks 180 degrees	FU exam: Vision
3	Left	2=No	2=No	2=No	1=Yes	1=Normal
	Right	2=No	2=No	2=No	1=Yes	1=Normal

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Early nutritional support and severity of illness paper
Date: Tuesday, October 20, 2009 9:28:26 AM

Richard
This paper provides a nice analysis to promote the use of early nutrition, particulalry enteral nutrition to enhance outcomes.

Specific comments-
My version is misisng an abstract and table 2.
The abstract should impress the point that nec rates are unaffected.

Thanks for putting this together!
Rose

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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support-- Piazza
Date: Monday, October 19, 2009 6:49:38 PM

Rose

On spreadsheet of abstract noted that Piazza secondary analysis of SUPPORT data was rejected. I thought this was put on hold pending analysis of primary data rather than rejected? If I am correct, can it be revised before spreadsheet is distributed at the Steering Comm meeting

BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

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From: Kimberley A Fisher
To: Zaterka-Baxter, Kristin
Cc: gloria.siaw@duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Re: Support Query (PD reports)
Date: Monday, October 19, 2009 5:16:54 PM
Attachments: PDs not reported on SUPP06 (Center 19) 19OCT09.rtf

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Here are the resolved queries.

Please let us know if you need anything else.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b) [redacted]
Email: kimberley.fisher@duke.edu

"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

10/19/2009 02:25 PM

To <gloria.siaw@duke.edu>, <Kimberley.fisher@duke.edu>
cc "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Gantz, Marie" <mgantz@rti.org>
Subject Support Query (PD reports)

Hi Gloria and Kim,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**
Thanks!
Kris

[attachment "PDs not reported on SUPP06 (Center 19) 19OCT09.rtf" deleted by Kimberley A Fisher/Pediatrics/mc/Duke]

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Surfactant not given in first hour (not reported on SUPP06)

Obs	Delivery Hospital	Infant Assignment	Delivery Date	Delivery Time	DR Intubation Performed	Indication for Intubation	Did the Infant Receive Surfactant in DR?
21	(b) (6)	Surfactant **Infant was given surf in DR-info was corrected in DMS.**	(b) (6)	22:02	Y	4=Randomization	Y
22	(b) (6)	CPAP **Given slightly out of window-SUPP06 completed and entered into DMS**	(b) (6)	19:58	Y	2=Resuscitation	Y

Obs	Received Surfactant	Received Surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
21	(b) (6)	0:06	Y	07/22/06	11:00
22		21:13	Y	11/13/06 **This was the first dose given in the NICU**	2:00

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Center 19

Oximeter not placed within two hours of NICU admission (not reported on SUPP06)

Data from SUPP04

Network number	Delivery date	NICU admission Date	NICU admission Time	Oximeter Placement Date	Oximeter Placement Time
(b) (6)	(b) (6) SUPP06 has been filled out to reflect this deviation. DMS has been updated.	(b) (6)	6:05	08/03/07	10:00
(b) (6)	(b) (6) SUPP06 has been filled out to reflect this deviation. DMS has been updated.	(b) (6)	6:20	07/14/08	5:58

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Center 19

Steriods for BPD given in first 21 days (not reported on SUPP06)

Network number	Delivery Date	Steroids for Chronic Lung Disease?	If YES, Date of First Dose
(b) (6)	[redacted] DAY Steroids given for RDS on (b) (6)		(b) (6)

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Gloria Siaw; Ronald N Goldberg; "Gantz, Marie"
Subject: Re: FW: Support
Date: Monday, October 19, 2009 3:50:09 PM
Attachments: BPD queries.rtf
SUPPORT ROP queries Center 19 16OCT09.rtf
Support.Queries.10.17.09.rtf

Here the resolved queries for our site.

Please let us know if you need anything else.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/19/2009 10:15 AM

To Ronald N Goldberg <goldb008@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, Michael Cotten <cotte010@mc.duke.edu>, Gloria Siaw <gloria.siaw@duke.edu>
cc "'Gantz, Marie'" <mgantz@rti.org>
Subject FW: Support

Here are the final missing queries for the Duke site as of last week's DMS transmission. Data lock will occur following tomorrow's transmission.

Thanks for all your help

Rose
[attachment "SUPPORT BPD queries Center 19 16OCT09.rtf" deleted by Kimberley A Fisher/Pediatrics/mc/Duke] [attachment "SUPPORT cross-form queries Center 19 16OCT09.doc" deleted by Kimberley A Fisher/Pediatrics/mc/Duke] [attachment "SUPPORT ROP queries Center 19 16OCT09.doc" deleted by Kimberley A Fisher/Pediatrics/mc/Duke]

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been entered through 8/18/05. DMS has been updated.**	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6) **Resolution: PHY01 has been corrected to match 36 weeks at (b) (6) DMS has been updated.**	**Resolved**

Center ID number=19=Duke University Network numbe (b) (6) Date of Birt (b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA (b) (6)

Query 1	Query 2	Query resolution Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6) **Resolution: The infant was incorrectly keyed as (b) (6) and was (b) (6) weeks at birth. The information has been corrected and keyed into the DMS.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6). **Resolution: SUPP11 has been keyed to include data through 9/18/05. The data has been entered into the DMS.**	Calculated date of 36 weeks PMA (09/18/05) does not match 36 week date on PHY01 (09/17/05). **Resolution: Date on PHY01 has been corrected to reflect correct date. All data has been entered into the DMS.**	**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA (b) (6)

Query 1	Query 2	Query resolution Center notes
Infant left hospital on (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: Supp11 forms have been entered through (b) (6) and the information has been entered into the DMS.**		**Resolved**

Center ID number=19=Duke University Network numbe (b) (6) Date of Birt (b) (6) Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution Center notes
Infant left hospital on (b) (6) per NG03 but SUPP11 forms are entered through (b) (6) **Resolution: NG03 has been changed to reflect the discharge date from DRH of (b) (6) The NG07 has also been rekeyed to reflect the 36 week status for this subject. All data has been updated in the DMS.**		**Resolved**

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 forms have been entered through (b) (6) and the information has been entered into the DMS.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was eligible for challenge per NG07-C but was not eligible per PHY01. If PHY01 was filled out incorrectly, please correct. **Resolution: PHY01 was filled out incorrectly and has since been changed to reflect the NG07. Infant was eligible for challenge but was not done due to error on PHY01 which made the child appear not eligible.**	Infant was on RA @36wks per NG07 and on vent/CPAP per PHY01. If infant was on RA by vent/CPAP Neil Finer would like to know why. Please respond with e **Resolution: Infant was on nasal cannula and PHY01 was incorrectly filled out. All data has been corrected and entered into the DMS.**	**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6). **Resolution: SUPP11 has been entered through (b) (6) NG03 has been corrected to reflect 36 weeks at 9/27/06. DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been filled out through (b) (6) which is (b) (6) weeks status as GA was keyed incorrectly and is now corrected. NG07 has been corrected. DMS has been updated.**	Infant was discharged on day of 36wks per NG03 but is missing 36wk snapshot on NG07. **Resolution: Infant was discharged to home on (b) (6) and 36 week status is (b) (6) Infant GA was incorrectly keyed and has been corrected. Therefore 36 week information is not required. DMS is updated.**	**Resolved**

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
On O2 not by NC/CPAP @ status per NG07 but on O2 by NC per SUPP11. If O2 was only by NC, delete FiO2 from NG07 and answer 'Y' to Q7. **Resolution: We went back and looked at this subject's chart and the highest Fi02 for status was 0.27. This information was recorded on the NG07 and SUPP11. Data has been entered on the NG07 and data has been entered into DMS.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: GA was keyed incorrectly. It should be (b) (6) (b) (6) weeks (b) (6) Information has been keyed into the DMS.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been entered through (b) (6). DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @status per NG07/SUPP11. Neil Finer would like to know why. Please respond with explanation. **Resolution: Infant was transferred to another hospital on NC. He was alternating CPAP and NC daily due to skin excoriations from CPAP. He was transferred on NC. SUPP11 has been updated. Information in DMS is correct.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
On O2 not by NC/CPAP @ status per NG07 but on O2 by NC per SUPP11. If O2 was only by NC, delete FiO2 from NG07 and answer 'Y' to Q7. **Resolution: Information has been updated on the NG07 to reflect this query. DMS has been updated.**		**Resolved**

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been updated through (b) (6) DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation. **Resolution: Infant was on CPAP RA. Infant has CLD. DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been entered through (b) (6) DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) **Resolution: SUPP11 has been entered through (b) (6) DMS has been updated.**		**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation. **Resolution: Infant was on CPAP RA. NG07 has been updated. Infant has CLD. Bronchoscopy on (b) (6) demonstrated no tracheomalacia. DMS has been updated.**		**Resolved**

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution Center notes
On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form. **Resolution: SUPP09 was incorrectly keyed with "Y" for threshold for the right eye on (b) (6) This information has been corrected and keyed into the DMS and sent to RTI.**					**Resolved**

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6) **Resolution: Correct discharge date is (b) (6) NG03 has been corrected and information entered into DMS and sent to RTI.**	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6) **Resolution: Correct discharge date is (b) (6). SUPP09 has been corrected and information entered into DMS and sent to RTI.**		**Resolved**

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09. **Resolution: IVH as incorrectly keyed from the NG03 and IVH 2 that is listed on the SUPP09 is correct. Information has been keyed into DMS and sent to RTI.**			**Resolved**

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution Center notes
SUPP02 treatment assignment (CPAP, blue) does not match that on randomization card (Surf, blue). **Resolution: Randomization was incorrectly keyed from the SUPP02 and the assignment was Surf, blue. Information has been corrected in DMS and sent to RTI.**			**Resolved**

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; nxs5@case.edu; mcw3@case.edu
Cc: mgantz@rti.org
Subject: RE: SUPPORT
Date: Monday, October 19, 2009 2:25:24 PM
Attachments: SUPPORT ROP queries Center 3 16OCT09 (2).rtf

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 17, 2009 8:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nxs5@case.edu; mcw3@po.cwru.edu; bss5@case.edu
Cc: mgantz@rti.org
Subject: RE: SUPPORT

Here are the ROP ones.

thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, October 17, 2009 8:29 AM
To: nxs5@case.edu; mcw3@po.cwru.edu; bss5@case.edu
Cc: mgantz@rti.org
Subject: SUPPORT

Hi,
Attached a SUPPORT missing data/queries. Data lock will occur following DMS transmission on Tuesday October 20. Please try to send all of the requested information at this time (or before).

Thanks for all your help!!!
Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

SUPPORT ROP Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Changed right eye threshold='Y' per MOP.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Error. Changed threshold='Y' per MOP on form for both eyes.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
On SUPP10 exam dated (b) (6) lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo.'	Error. Highest stage should be 6=Post laser/cryo. Corrected.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.	Error. Should be laser surgery for both eyes. Corrected.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.	Error. Both eyes are mature (zone=4). Corrected.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.	Error. ROP on NGO3 should be **'No'**. Corrected

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Error. Changed threshold='Y' per MOP. Corrected.

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.	**Query 1/Query 2**-Eye exams on (b) (6) - changed threshold value per MOP (i.e. not using ophthalmologists remarks). **Query 3**-correct as recorded. Surgery only right eye.

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From: Zaterka-Baxter, Kristin
To: Johnson, Karen
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:29:35 PM
Attachments: PDs not reported on SUPP06 (Center 24) 19OCT09.rtf
Importance: High

Hi Karen,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 24

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR intubation successful	Indication for intubation	Did the infant receive surfactant in DR?
24	(b) (6)	CPAP	12/18/06	21:39	Y	2=Resuscitation	N
25		CPAP	01/02/07	18:34	Y	2=Resuscitation	N
26		CPAP	01/02/07	18:36	Y	2=Resuscitation	N
27		Surfactant	01/30/08	12:48	Y	2=Resuscitation	N
28		CPAP	02/08/08	9:49	Y	2=Resuscitation	N
29		Surfactant	05/11/08	3:13	Y	2=Resuscitation	N
30		CPAP	02/10/09	23:45	Y	2=Resuscitation	N

Obs	Received surfactant Date	Received surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
24	.	.	Y	12/18/06	22:59
25	.	.	Y	01/02/07	21:13
26	.	.	Y	01/02/07	20:57
27	.	.	Y	01/30/08	14:12
28	.	.	Y	02/08/08	11:04
29	.	.	Y	05/11/08	5:07
30	.	.	N	.	.

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From: Zaterka-Baxter, Kristin
To: BMackinnon@tuftsmedicalcenter.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:28:30 PM
Attachments: PDs not reported on SUPP06 (Center 23) 19OCT09.rtf
Importance: High

Hi Brenda,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Surfactant not given in first hour (not reported on SUPP06)

Obs	Newborn number	Position in Assignment	Delivery Date	Delivery Time	DR intubation successful	Indication for intubation	Did the infant receive surfactant in DR?
21	(b) (6)	CPAP	(b) (6)	10:45	Y	2=Resuscitation	Y

Obs	Received surfactant	Received surfactant Date	Received surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
23		(b) (6)	12:00	N	.	.

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From: Zaterka-Baxter, Kristin
To: wrich@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:25:50 PM
Attachments: PDs not reported on SUPP06 (Center 22) 19OCT09.rtf
Importance: High

Hi Wade,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Steriods for BPD given in first 21 days (not reported on SUPP06)

Network number	Delivery Date	Steroids for Chronic Lung Disease?	If YES, Date of First Dose
(b) (6)	(b) (6)	Y	12/10/08

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From: Zaterka-Baxter, Kristin
To: gloria.siaw@duke.edu; Kimberley.fisher@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:25:04 PM
Attachments: PDs not reported on SUPP06 (Center 19) 19OCT09.rtf
Importance: High

Hi Gloria and Kim,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 19

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation successful	Indication for Intubation	Did the infant receive surfactant in DR?
21	(b) (6)	Surfactant	(b) (6)	22:02	Y	4=Randomization	Y
22		CPAP		19:58	Y	2=Resuscitation	Y

Obs	Received surfactant - Date	Received surfactant - Time	Was Surfactant given in NICU	Surfactant Dose 1 - Date	Surfactant Dose 1 - Time
21	(b) (6)	0:06	Y	(b) (6)	11:00
22		21:13	Y		2:00

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Center 19

Oximeter not placed within two hours of NICU admission (not reported on SUPP06)

Data from SUPP04

Network number	Delivery Date	NICU admission Date	NICU admission Time	Oximeter Placement Date	Oximeter Placement Time
(b) (6)	(b) (6)	(b) (6)	6:05	(b) (6)	10:00
[redacted]	(b) (6)	(b) (6)	6:20	(b) (6)	5:58

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Center 19

Steriods for BPD given in first 21 days (not reported on SUPP06)

Network number	Delivery Date	Steroids for Chronic Lung Disease?	If YES Date of First Dose
(b) (6)	(b) (6)	Y	(b) (6)

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From: Zaterka-Baxter, Kristin
To: Mcdavid, Georgia E
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:23:25 PM
Attachments: PDs not reported on SUPP06 (Center 18) 19OCT09.rtf
Importance: High

Hi Georgia,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 18

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation successful	Indication for intubation	Did the infant receive surfactant in DR?
20	(b) (6)	CPAP	(b) (6)	18:26	Y	2=Resuscitation	N

Obs	Received surfactant Date	Received surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
20	.	.	Y	(b) (6)	20:15

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Center 18

Steriods for BPD given in first 21 days (not reported on SUPP06)

Network number	Delivery Date	Steroids for Chronic Lung Disease?	If YES, Date of First Dose
(b) (6)	(b) (6)	T	(b) (6)

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From: Zaterka-Baxter, Kristin
To: Hensman, Angelita
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: FW: Support Query (PD reports)
Date: Monday, October 19, 2009 2:22:23 PM
Attachments: PDs not reported on SUPP06 (Center 14) 19OCT09.rtf
Importance: High

Hi Angelita,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 14

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation successful	Indication for intubation	Did the infant receive surfactant in DR?
12	(b) (6)	Surfactant	(b) (6)	21:21	Y	4=Randomization	N
13		CPAP		10:23	Y	2=Resuscitation	N
14		CPAP		16:38	Y	2=Resuscitation	N
15		CPAP		9:11	Y	2=Resuscitation	N
16		CPAP		22:50	Y	2=Resuscitation	N
17		CPAP		5:12	Y	2=Resuscitation	N
18		CPAP		22:12	Y	2=Resuscitation	N
19		CPAP		13:42	Y	2=Resuscitation	N

Obs	Received Surfactant Date	Received Surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
12	.	.	Y	(b) (6)	22:35
13	.	.	Y		11:36
14	.	.	Y		18:10
15	.	.	Y		11:30
16	.	.	Y		0:45
17	.	.	Y		7:15
18	.	.	Y		3:30
19	.	.	Y		15:00

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From: Zaterka-Baxter, Kristin
To: monica.konstantino@yale.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: FW: Support Query (PD reports)
Date: Monday, October 19, 2009 2:21:25 PM
Attachments: PDs not reported on SUPP06 (Center 13) 19OCT09.rtf
Importance: High

Hi Monica,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 13

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation successful	Indication for intubation	Did the infant receive surfactant in DR?
11	(b) (6)	CPAP	(b) (6)	4:30	Y	2=Resuscitation	N

Obs	Received surfactant Date	Received surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
11	.	.	Y	(b) (6)	6:00

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From: Zaterka-Baxter, Kristin
To: grisbyca@email.uc.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:20:45 PM
Attachments: PDs not reported on SUPP06 (Center 11) 19OCT09.rtf
Importance: High

Hi Cathy,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 11

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation Successful	Indication for intubation	Did the infant receive surfactant in DR?
10	(b) (6)	CPAP	(b) (6)	23:30	Y	2=Resuscitation	N

Obs	Received surfactant - Date	Received surfactant - Time	Was Surfactant given in NICU	Surfactant Dose 1 - Date	Surfactant Dose 1 - Time
10	.	.	Y	(b) (6)	0:45

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Center 11

Steriods for BPD given in first 21 days (not reported on SUPP06)

Network number	Delivery Date	Steroids for Chronic Lung Disease?	If YES, Date of First Dose
(b) (6)	(b) (6)	Y	(b) (6)

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From: Zaterka-Baxter, Kristin
To: nancy newman
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: FW: Support Query (PD reports)
Date: Monday, October 19, 2009 2:18:46 PM
Attachments: PDs not reported on SUPP06 (Center 3) 19OCT09.rtf
Importance: High

Hi Nancy,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Center 3

Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation Successful	Indication for Intubation	Did the infant receive surfactant in DR?
1	(b) (6)	CPAP	(b) (6)	13:41	Y	2=Resuscitation	N
2		CPAP		5:07	Y	2=Resuscitation	N
3		CPAP		8:49	Y	2=Resuscitation	N
4		CPAP		16:29	Y	2=Resuscitation	N
5		Surfactant		12:53	Y	4=Randomization	N
6		CPAP		3:03	Y	2=Resuscitation	N

Obs	Received surfactant - Date	Received surfactant - Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
1	.	.	Y	(b) (6)	15:50
2	.	.	Y		6:55
3	.	.	Y		10:00
4	.	.	Y		18:00
5	.	.	Y		14:10
6	.	.	Y		4:30

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From: Zaterka-Baxter, Kristin
To: karen.osborne@hsc.utah.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Query (PD reports)
Date: Monday, October 19, 2009 2:17:33 PM
Attachments: PDs not reported on SUPP06 (Center 25) 19OCT09.rtf
Importance: High

Hi Karen,

Attached please find a query of protocol deviations that appear on other forms but are not reported on SUPP06. Please review this list and amend data where needed. Please be reminded that **Support data lock is 10/20/09.**

Thanks!
Kris

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Surfactant not given in first hour (not reported on SUPP06)

Obs	Network number	Treatment Assignment	Delivery Date	Delivery Time	DR Intubation successful	Indication for Intubation	Did the infant receive surfactant in DR?
31	(b) (6)	CPAP	(b) (6)	19:51	Y	2=Resuscitation	N
32		Surfactant		1:36	Y	2=Resuscitation	N
33		CPAP		13:27	Y	2=Resuscitation	Y

Obs	Received surfactant Date	Received surfactant Time	Was Surfactant given in NICU	Surfactant Dose 1 Date	Surfactant Dose 1 Time
31	.	.	Y	(b) (6)	23:00
32	.	.	N	.	.
33	(b) (6)	14:45	N	.	.

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Oximeter not placed within two hours of NICU admission (not reported on SUPP06)

Data from SUPP04

Network number	Delivery Date	NICU admission Date	NICU admission Time	Oximeter Placement Date	Oximeter Placement Time
(b) (6)	(b) (6)	(b) (6)	23:47	(b) (6)	2:15
			23:48		2:15
			23:49		2:15

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From: Zaterka-Baxter, Kristin
To: goldb008@mc.duke.edu; Michael Cotten; Kimberley.fisher@duke.edu; gloria.siaw@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Gantz, Marie
Subject: FW: Duke report
Date: Monday, October 19, 2009 12:17:01 PM
Attachments: SUPPORT data for Duke visit 16OCT09.doc

Dear all,

Attached please find the final Support primary outcomes verification report. Please verify that the data for each case is correct by initially next to the data in the provided column. Please note there is only one field for initials per ID (in the ROP report); by initially her it means you have verified both the BPD and ROP data against the medical records. Please scan the completed report and send it to Dr. Higgins (please copy me for our records).

In addition, if you have not already received them, Dr. Higgins will be sending ROP, BPD and cross-form queries which require your immediate attention. Please note that we have added gestational age to the BPD queries; there are several infants who have different GA data for Support which do not match the NG02. Please verify the GA of these infants.

Thanks
Kris

Kris Zaterka-Baxter
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SUPPORT Data for Duke Visit 16OCT09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (physiologic definition)	BPD (physician) data source	Reason for BPD (physician) determination	BPD (supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	FU note
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	Y	PHY02RA/NG07v3C	Challenge result	Y	NG07	On supplemental O2 @36wks	
(b) (6)	[redacted]	Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
[redacted]	(b) (6)	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
[redacted]	(b) (6)	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	

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SUPPORT Data for Duke Visit 16OCT09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (phys def) determination	BPD (phys def) data source	Reason for BPD (phys def) determination	BPD (supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	RT note
(b) (6)	[redacted]	Transferred	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	Y	NG07	On supplemental O2 @36wks	
(b) (6)	[redacted]	Discharged on day of 36 wks PMA	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Discharged	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	Y	NG07	On supplemental O2 @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	Y	SUPP11	On vent/CPAP @status	N	NG07	RA @status	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	

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SUPPORT Data for Duke Visit 16OCT09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (physiologic definition)	BPD (physician determination) data source	Reason for BPD (physician) determination	BPD supplemental O2	BPD (O2) data source	Reason for BPD (O2) determination	Footnote
[redacted]	(b) (6)	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	NG07 36wk snapshot has been deleted
(b) (6)	[redacted]	Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
(b) (6)	[redacted]	Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
(b) (6)	[redacted]	Transferred	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	Y	NG07	On vent/CPAP @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	

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SUPPORT Data for Duke Visit 16OCT09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (physiologic definition)	BPD (physician) data source	Reason for BPD (physician) determination	BPD (supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	RT note
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	Y	NG07	On vent/CPAP @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)	[redacted]	Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	

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SUPPORT Data for Duke 16OCT09 (ROP Data)

Network number	Final status	Left eye ROP (Y/N)	Left eye ROP	Left eye ROP location	Right eye ROP (Y/N)	Right eye ROP	Right eye ROP location	Pi initials
(b) (6)	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Death	.	.	.	.	.	.	
	Discharged	Y	Y	ROP surgery	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = mature	

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SUPPORT Data for Duke 16OC109 (ROP Data)

Network number	final status	Left eye ROP (final)	Left eye ROP	Left eye ROP location	Right eye ROP (final)	Right eye ROP	Right eye ROP location	PI initials
(b) (6)	Discharged	N	.	.	N	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	ROP surgery	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
(b) (6)	Death	.	.	.	.	.	.	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; nxs5@case.edu; mcw3@case.edu
Cc: mgantz@rti.org
Subject: RE: SUPPORT
Date: Monday, October 19, 2009 11:01:35 AM
Attachments: SUPPORT BPD queries Center 3 16OCT09.rtf

Please note that Michele's email is mcw3@case.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 17, 2009 8:29 AM
To: nxs5@case.edu; mcw3@po.cwru.edu; bss5@case.edu
Cc: mgantz@rti.org
Subject: SUPPORT

Hi,
Attached a SUPPORT missing data/queries. Data lock will occur following DMS transmission on Tuesday October 20. Please try to send all of the requested information at this time (or before).

Thanks for all your help!!!
Rose
Rosemary D. Higgins, MD
Program Scientist for the NICHD Neonatal Research Network

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SUPPORT BPD Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1 -SMITH A	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (07/15/06) does not match 36 week date on PHY01 (b) (6)		Correct as entered. Date of evaluation is (b) (6)

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1 -SMITH B	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (07/15/06) does not match 36 week date on PHY01 (b) (6)		Error. Date of PHY01 should be (b) (6) Corrected.

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1 -HAMLETT	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		Error. Date of PHY01 should be (b) (6) Corrected.

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1 -WARREN	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		Error. Data entered on wrong patient. PHY01 deleted for this patient. PHY01 entered for ID# (b) (6)

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1 -STEVENS	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		Baby had severe PPHN/BPD. Was vent./CPAP dependent for the entire 120 days and off O_2 for only 7 days. Was on room air at time of 36 weeks.

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From: Gantz, Marie
To: Zaterka-Baxter, Kristin; goldb008@mc.duke.edu; Michael Cotten; Kimberley.fisher@duke.edu; gloria.siaw@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie
Subject: RE: Duke report
Date: Monday, October 19, 2009 12:22:34 PM

Just to clarify, the BPD query responses which we previously received from Duke noted gestational ages that differed from what is entered on the NG02. This resulted in different dates for 36 weeks PMA being calculated by the center and by RTI. In the latest queries from Friday we have included the GA as it is entered on the NG02 so that you can check it against your records. Thanks very much for your help resolving these queries. If you have specific questions about the queries please contact me.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Zaterka-Baxter, Kristin
Sent: Monday, October 19, 2009 12:17 PM
To: 'M. D. Ronald Goldberg (goldb008@mc.duke.edu)'; 'Michael Cotten'; 'Kimberley.fisher@duke.edu'; Gloria Siaw (gloria.siaw@duke.edu)
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Huitema, Carolyn Petrie; Gantz, Marie
Subject: FW: Duke report

Dear all,

Attached please find the final Support primary outcomes verification report. Please verify that the data for each case is correct by initially next to the data in the provided column. Please note there is only one field for initials per ID (in the ROP report); by initially her it means you have verified both the BPD and ROP data against the medical records. Please scan the completed report and send it to Dr. Higgins (please copy me for our records).

In addition, if you have not already received them, Dr. Higgins will be sending ROP, BPD and cross-form queries which require your immediate attention. Please note that we have added gestational age to the BPD queries; there are several infants who have different GA data for Support which do not match the NG02. Please verify the GA of these infants.

Thanks
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

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Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support
Date: Monday, October 19, 2009 9:25:20 AM
Attachments: SUPPORT BPD queries Center 19 16OCT09.rtf
SUPPORT cross-form queries Center 19 16OCT09.doc
SUPPORT ROP queries Center 19 16OCT09.doc

Thanks, Rose. Here are the Duke queries.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 17, 2009 8:54 AM
To: Gantz, Marie
Subject: Support

Marie
I finally got the SuUPPORT reminder out (via dial up- something is wrong with my computer)

I somehow lost the email with the Duke BPD missing queries- can you resend??
Thanks
Rose

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (08/18/05).		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant left hospital on (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant left hospital on (b) (6) per NG03 but SUPP11 forms are entered through (b) (6)		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was eligible for challenge per NG07-C but was not eligible per PHY01. If PHY01 was filled out incorrectly, please correct.	Infant was on RA @36wks per NG07 and on vent/CPAP per PHY01. If infant was on RA by vent/CPAP Neil Finer would like to know why. Please respond with e	

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Infant was discharged on day of 36wks per NG03 but is missing 36wk snapshot on NG07.	

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
On O2 not by NC/CPAP @ status per NG07 but on O2 by NC per SUPP11. If O2 was only by NC, delete FiO2 from NG07 and answer 'Y' to Q7.		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @status per NG07/SUPP11. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
On O2 not by NC/CPAP @ status per NG07 but on O2 by NC per SUPP11. If O2 was only by NC, delete FiO2 from NG07 and answer 'Y' to Q7.		

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through 08/14/08.		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) ((b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)		

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP02 treatment assignment (CPAP, blue) does not match that on randomization card (Surf, blue).			

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network numbe(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.					

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org
Subject: RE: ROP queries
Date: Friday, October 16, 2009 4:51:33 PM
Attachments: ROP queries 16OCT09.zip
BPD queries 16OCT09.zip
Cross-form queries 16OCT09.zip

Rose,

Attached are zipped files with queries for BPD, ROP and the cross-form checks. I've tweaked the queries slightly, so there may be some new ones. Thanks, as always, for sending them out.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 16, 2009 12:00 PM
To: Gantz, Marie; Das, Abhik
Subject: ROP queries

Do you think I should send individual site reminders or a generic email to all sites - data lock on tuesday!!

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SUPPORT ROP Queries for Center 25-University of Utah

Center ID number=25=University of Utah Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Thank you for entering F5 to confirm two exams in zone 3 with stage 3 ROP in the last exam. Although this meets criteria for final status, if additional exams are available for the infant, please enter them.					

Center ID number=25=University of Utah Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Thank you for entering F5 to confirm two exams in zone 3 with stage 3 ROP in the last exam. Although this meets criteria for final status, if additional exams are available for the infant, please enter them.					

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SUPPORT ROP Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo.'					

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.					

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.					

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.					

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SUPPORT ROP Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Center ID number=3=Case Western University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.			

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SUPPORT ROP Queries for Center 4-University of Texas-Dallas

Center ID number=4=University of Texas-Dallas Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.					

Center ID number=4=University of Texas-Dallas Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 one or both eyes went from stage 2 or 3 ROP to mature within a week. If this is correct, please F5 to confirm.	Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.				

Center ID number=4=University of Texas-Dallas Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date ((b) (6)					

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SUPPORT ROP Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated [redacted] right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.					

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.					

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SUPPORT ROP Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.				

Center ID number=5=Wayne State University Network number=7(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	

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SUPPORT ROP Queries for Center 8-University of Miami

Center ID number=8=University of Miami Network number=7(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

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SUPPORT ROP Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.					

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.					

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.					

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated 10/11/07 right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.			

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SUPPORT ROP Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

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SUPPORT ROP Queries for Center 11-University of Cincinnati

Center ID number=11=University of Cincinnati Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.	Per NG03 right eye had an exam with ROP stage 1 in zone 1 but that is not reflected on the SUPP10.				

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SUPPORT ROP Queries for Center 13-Yale University

Center ID number=13=Yale University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Thank you for entering F5 to confirm two exams in zone 3 with stage 3 ROP in the last exam. Although this meets criteria for final status, if additional exams are available for the infant, please enter them.					

Center ID number=13=Yale University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Thank you for entering F5 to confirm two exams in zone 3 with stage 3 ROP in the last exam. Although this meets criteria for final status, if additional exams are available for the infant, please enter them.					

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SUPPORT ROP Queries for Center 14-Brown University

Center ID number=14=Brown University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye highest ROP stage in lowest zone is > highest stage in any zone.	Per NG03 plus disease was diagnosed but that is not reflected on the SUPP10.				

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SUPPORT ROP Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10.	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10.				

Center ID number=16=University of Alabama Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 3 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 2 in zone 3 but per SUPP10 highest stage in that zone was 0.				

Center ID number=16=University of Alabama Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=16=University of Alabama Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.				

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SUPPORT ROP Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 0.				

Center ID number=18=University of Texas-Houston Network number(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated 02/05/06 left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=18=University of Texas-Houston Network number(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 surgery was performed for ROP but that is not reflected on the SUPP10.					

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SUPPORT ROP Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm. Also, if additional exams are available for the infant, please enter them.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm. Also, if additional exams are available for the infant, please enter them.			

Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

Center ID number=18=University of Texas-Houston Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.					

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SUPPORT ROP Queries for Center 20-Wake Forest University

Center ID number=20=Wake Forest University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.					

Center ID number=20=Wake Forest University Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.				

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SUPPORT ROP Queries for Center 23-Tufts University

Center ID number=23=Tufts University Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.				

Center ID number=23=Tufts University Network number(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

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SUPPORT ROP Queries for Center 24-University of Iowa

Center ID number=24=University of Iowa Network number=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye highest ROP stage in lowest zone is > highest stage in any zone.					

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SUPPORT BPD Queries for Center 26-University of New Mexico

Center ID number=26=University of New Mexico Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6)) does not match 36 week date on PHY01 (b) (6)		

Center ID number=26=University of New Mexico Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Reason not challenged on NG07-C (4) does not match reason on PHY01 (1).		

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SUPPORT BPD Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA=(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA=(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA=(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA=(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

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SUPPORT BPD Queries for Center 4-University of Texas-Dallas

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth(b) (6) 9 Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

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SUPPORT BPD Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6).	Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.	

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Number of days on O2 @36wks per NG07 (76) is greater than DOL @36wks (75).	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

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SUPPORT BPD Queries for Center 8-University of Miami

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant left hospital after 14 days per NG03 but no SUPP11 forms have been entered.		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6).	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

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SUPPORT BPD Queries for Center 8-University of Miami

Center ID number=8=University of Miami Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=1 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks(b) (6) NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through(b) (6)	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=6 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 8-University of Miami

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
On support @36wks per NG07 but off support all day per SUPP11.		

Center ID number=9=Emory University Network numbe(b) (6) Date of (b) (6) Gestational Age (weeks)=26 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
On O2 by NC @36wks per NG07 but on RA by NC with flow<=.5 at all time points on SUPP11. If both forms are correct please F5 on NG07 to verify O2 by NC		

Center ID number=9=Emory University Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=6 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

Center ID number=9=Emory University Network numbe(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=5 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)		

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SUPPORT BPD Queries for Center 11-University of Cincinnati

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=11=University of Cincinnati Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
On support @36wks per NG07 but off support all day per SUPP11.	Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	

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SUPPORT BPD Queries for Center 12-Indiana University

Center ID number=12=Indiana University Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY0 (b) (6)		

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=12=Indiana University Network numbe(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY0 (b) (6)		

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=0 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 12-Indiana University

Center ID number=12=Indiana University Network numbe(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=12=Indiana University Network number(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA(b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=12=Indiana University Network numbe(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Off O2 @36wks per NG07 but on O2 per SUPP11. NG07 should record highest level of support for the day.		

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SUPPORT BPD Queries for Center 13: Yale University

Center ID number=13=Yale University Network numbe(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=13=Yale University Network number(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=13=Yale University Network number(b) (6) Date of Birth(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=3 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 14-Brown University

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

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SUPPORT BPD Queries for Center 15-Stanford University

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

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SUPPORT BPD Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 20-Wake Forest University

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=6 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 22-University of California-San Diego

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=2 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=4 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=22=University of California-San Diego Network number(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=0 Date of 36 weeks PMA(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 23-Tufts University

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=23=Tufts University Network number=66771 Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=25 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 24-University of Iowa

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=3 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=0 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)	Infant was on RA @36wks per NG07 and on vent/CPAP per PHY01. If infant was on RA by vent/CPAP Neil Finer would like to know why. Please respond with e	

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=26 Gestational Age (days)=6 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=1 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT BPD Queries for Center 25-University of Utah

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=11/16/06 Gestational Age (weeks)=27 Gestational Age (days)=5 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=27 Gestational Age (days)=2 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Infant was on RA by vent/CPAP @36wks per NG07. Neil Finer would like to know why. Please respond with explanation.		

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6) Gestational Age (weeks)=24 Gestational Age (days)=4 Date of 36 weeks PMA=(b) (6)

Query 1	Query 2	Query resolution: Center notes
Calculated date of 36 weeks PMA (b) (6) does not match 36 week date on PHY01 (b) (6)		

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SUPPORT Cross-Form Queries for Center 18-University of Texas-Houston

Center ID number=18 Network number=[redacted] NG02 birth date=[redacted]

Query 1	Query 2	Query 3	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) [redacted] is different from discharge date (Q N.1.) [redacted]	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different [redacted] vs [redacted]		

Center ID number=18 Network number=[redacted] NG02 birth date=[redacted]

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP03 and/or NG02 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=18 Network number=[redacted] NG02 birth date=[redacted]

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG02.	Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.		

Center ID number=18 Network number=[redacted] NG02 birth date=[redacted]

Query 1	Query 2	Query 3	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.		

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)		

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP02 treatment assignment (CPAP, blue) does not match that on randomization card (Surf, blue).			

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SUPPORT Cross-Form Queries for Center 22-University of California-San Diego

Center ID number=22 Network number=(b) (6) NG02 birth date=0(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.)(b) (6) is different from discharge date (Q N.1.) (b) (6)			

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SUPPORT Cross-Form Queries for Center 5-Wayne State University

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP04 surfactant date/time(b) (6) :21:35:00) does not match NG03 surfactant date/time(b) (6) :21:55:00).	Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.		

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP04 surfactant date/time(b) (6) :16:35:00) does not match NG03 surfactant date/time(b) (6) 17:30:00).			

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Infant intubated in DR per NG02 but was not intubated in DR per SUPP03.			

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SUPPORT Cross-Form Queries for Center 8-University of Miami

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP02 treatment assignment (CPAP, orange) does not match that on randomization card (CPAP, blue).			

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SUPPORT Cross-Form Queries for Center 9-Emory University

Center ID number=9 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 15 but PVL is not recorded on SUPP09.			

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SUPPORT Cross-Form Queries for Center 11-University of Cincinnati

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.			

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 10 but severe IVH is not recorded on NG03.			

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]; Adams-Chapman, Ira; Barbara Stoll; Ira Adams-Chapman; Buchter, Susie
Cc: "Gantz, Marie"
Subject: RE: SUPPORT!!!
Date: Friday, October 16, 2009 12:27:46 PM
Attachments: SUPPORT ROP queries Center 9 09OCT09[1].rtf

Rose,
We have attached our responses to the queries. We have our computer back and we are in the process of entering all data and will transmit today.

I think we have exhaused all efforts. We will continue to look for these children and hopefully find for follow-up. See below:
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

Hi,

Attached are ROP and BPD queries. We are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study. Many of these are previously "excused," but we still have no firm ROP outcome on these infants. If you have any way of determining ROP outcome, please let us know. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. Cannot locate.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Cannot locate
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Cannot locate
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Family thinks they have moved to LA but do not know where.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Cannot locate. Child was in foster care and now back with mom. Cannot find her.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Cannot locate.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. Cannot locate.

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Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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SUPPORT ROP Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								Correct & confirmed

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								Correct & confirmed

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated 06/22/07 right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							Both eyes coded as Threshold

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								Correct & confirmed

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								Coded as Threshold

Center ID number=9=Emory University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.						Coded as Thres-hold

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SUPPORT ROP Queries for Center 9-Emory University

Query resolution center notes

Center ID number=9=Emory University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							Coded as Threshold

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20
Date: Wednesday, October 14, 2009 10:19:32 PM

Rose,
Don't know if we can find any more of the 6 children needing ROP exams. Will not give up till Monday.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 3:00 PM
To: Hale, Ellen
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Ellen
We have that this infant was withdrawn on day 11, correct? If so, we don't (can't get) need anything else for this one

Thanks for all your help
Rose

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Wednesday, October 14, 2009 2:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,
I was thinking we needed more ROP info on this baby but it is not on ROP list.
I think we are ok with ROP outcome.
Baby is on lost to follow up and we cannot locate. Call me at 404-778-1679.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 2:16 PM
To: Hale, Ellen; 'Gantz, Marie'; Ellen Hale; Barbara Stoll
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20
Please let us know if we can use GDB information on this child.

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Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 14, 2009 2:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

We queried centers that had infants withdrawn from the study to find out whether we could use their data, but I do not see a response from Emory. Apparently, some centers can still use the GDB data even if SUPPORT data were not collected after withdrawal. We need to know from the center what we are allowed to use per their IRB and consent for GDB vs. SUPPORT.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org<mailto:mgantz@rti.org>

828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 1:43 PM
To: Gantz, Marie
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT DATA LOCK DATE - OCTOBER 20

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From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Wednesday, October 14, 2009 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,

Should (b) (6) 1 be removed from outcome information? This is the mother that withdrew consent and further data collection?

Ellen

Ellen Hale, RN, BS, CCRC

Neonatal Research Network

Emory University School of Medicine

Department of Pediatrics - Division of Neonatology

Office: 404-778-1679

Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, October 13, 2009 9:04 AM
To: Hale, Ellen; Finer, Neil; Rich, Wade; 'Duara, Shahnaz'; 'Reubens, Linda'; Everett-Thomas, Ruth; 'Phelps, Dale'; 'Michael O`Shea'; 'Nancy Peters'; (Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>); (rohls@unm.edu<mailto:rohls@unm.edu>); aaf2@po.cwru.edu<mailto:aaf2@po.cwru.edu>; Abhik Das; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Ambal (ambal@uab.edu<mailto:ambal@uab.edu>); Brad Yoder (Bradley.yoder@hsc.utah.edu<mailto:Bradley.yoder@hsc.utah.edu>); Brenda Poindexter; Carlo Waldemar

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(E-mail); cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Barbara Stoll; Tyson Jon (E-mail); VanMeurs, Krisa; (gloria.siaw@duke.edu<mailto:gloria.siaw@duke.edu>); (Karen.Osborne@hsc.utah.edu<mailto:Karen.Osborne@hsc.utah.edu>); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org<mailto:bmackinnon@tuftsmedicalcenter.org>); Cathy Grisby (cathy.grisby@uc.edu<mailto:cathy.grisby@uc.edu>); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu<mailto:karen-johnson@uiowa.edu>); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu<mailto:monica.konstantino@yale.edu>; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; Cunningham, Meg; Auman, Jeanette O.
Subject: SUPPORT DATA LOCK DATE - OCTOBER 20

Hi,

REMINDER: SUPPORT Dataset for acute outcomes with be LOCKED following DMS transmission on October 20

Please insure that you have all of your queries and edits answered.

Thanks for all the help on this trial.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "ahensman@wihri.org"; "mgantz@rti.org"
Cc: "alaptook@WIHRI.org"; "airene@rti.org"
Subject: Re: SUPPORT ROP queries Center 14 09OCT09
Date: Wednesday, October 14, 2009 6:09:35 PM

Thanks
Rose

From: Hensman, Angelita <AHensman@WIHRI.org>
To: 'Gantz, Marie' <mgantz@rti.org>
Cc: Laptook, Abbot <ALaptook@WIHRI.org>; 'Irene, Amanda' <airene@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Irene, Amanda <airene@rti.org>
Sent: Wed Oct 14 17:13:13 2009
Subject: RE: SUPPORT ROP queries Center 14 09OCT09

(b) (6) NG03 changed to "No plus disease". Confirmed with ophthalmologist. SUPP10 is correct. Will be entered and transmitted on Friday (10/16). This should complete all the SUPPORT edits for Brown.

Angelita

From: Hensman, Angelita
Sent: Tuesday, October 13, 2009 12:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Gantz, Marie'; Laptook, Abbot; Irene, Amanda
Subject: RE: SUPPORT ROP queries Center 14 09OCT09

Resolution to ROP edits attached. I was not able to answer one on # (b) (6) I need to find out if "Early dilation" per exam under plus disease constitutes Plus disease".
Will send that in as soon as I get an answer.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 5:05 PM
To: Laptook, Abbot; Hensman, Angelita
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 14 09OCT09

Hi,
We are missing a few SUPPORT outcomes - The final date for data transmission is October 20.

thanks for all the help

Rose

14	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14	[redacted]	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kimberley A Fisher"
Cc: "Michael Cotten"; "Ronald N Goldberg"; "kzaterka@rti.org"
Subject: RE: Responses to Site Monitoring Visits 9.2.09 and 9.29.09
Date: Wednesday, October 14, 2009 4:44:00 PM

You can make a pdf and send it to both of us via email. I will be out of the office tomorrow and Friday

Thanks
Rose

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Wednesday, October 14, 2009 4:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Ronald N Goldberg; kzaterka@rti.org
Subject: RE: Responses to Site Monitoring Visits 9.2.09 and 9.29.09

Dr Higgins and Kris
I have not as yet sent out the packet of information but plan on sending it out no later than tomorrow morning. I will provide the tracking information to both of you. Should I make 2 copies and send a package to both of you or where should I sent it?

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b) (6)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/14/2009 03:59 PM

To "'Kimberley A Fisher" <kimberley.fisher@duke.edu>, Ronald N Goldberg <goldb008@mc.duke.edu>, Michael Cotten <cotte010@mc.duke.edu>
cc "kzaterka@rti.org" <kzaterka@rti.org>
Subject RE: Responses to Site Monitoring Visits 9.2.09 and 9.29.09

Kim
I did not receive anything from FED EX. Do you have a tracking number?

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Also, we need a response to the following items by Monday:

Action items requiring a response to NICHD by October 19, 2009:

1. The collection of research data at DRH needs to be addressed and resolved so that source document can be obtained on infants in observational studies and trials to have complete data in the DMS.
2. A written plan for the process and resolution of edits and queries needs to be formulated and instituted at the Duke site detailing responsibility for staff completing the entry to RTI. This must be sent to NICHD.

a. All SUPPORT missing forms, batch edits, queries and action items listed below must be resolved immediately.

3. Duke is required to have all SUPPORT study primary outcomes for all 64 cases verified and the Primary Outcomes Report signed by Dr. Goldberg and/or Dr. Cotten to ensure the integrity of the data.

a. In addition, it is imperative that all data and neuro-images be sent to RTI immediately for the Support Neurodevelopmental Secondary Study. There are currently 2 infants with missing MRI images (b) (6))

4. A Weekly meeting for the NRN research staff (PI, alternate PI, Follow Up PI, clinical research director, research coordinator, research staff and data entry staff) is recommended to facilitate communication, resolution of current outstanding data, and ongoing protocol updates as well as other items relevant to NRN research.
5. The establishment of a communication plan for the Rochester site conducting the SUPPORT Secondary Breathing Outcomes interviews is requested. Ms. Zaterka-Baxter will Assist Dr. Fisher and send the necessary information to establish this process. The Breathing Outcomes FU windows for all patients are posted to the private NRN gateway.

Thanks
Rose

From: Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]
Sent: Monday, October 12, 2009 4:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg; Michael Cotten
Cc: kzaterka@rti.org
Subject: Responses to Site Monitoring Visits 9.2.09 and 9.29.09

Dear Dr. Higgins and Kris,
Enclosed are the responses to the two monitoring visits that were done for the NICHD/NRN. We will be sending both of these reports by FedEx tomorrow along with all the supporting documentation that was requested. Please let us know if there are any additional requirements needed.

Site Visit 9.2.09

Site Visit 9.29.09

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Thank you,
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970(b) (6)
Email: kimberley.fisher@duke.edu

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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Gantz, Marie"; Ellen Hale; Das, Abhik; Zaterka-Baxter, Kristin
Subject: Re: SUPPORT DATA LOCK DATE - OCTOBER 20
Date: Wednesday, October 14, 2009 5:31:41 PM

I believe Ellen has already sent you info on the one baby-- used GDB info

BJS**"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:**
Please let us know if we can use GDB information on this child.

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 14, 2009 2:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

We queried centers that had infants withdrawn from the study to find out whether we could use their data. We do not see a response from Emory. Apparently, some centers can still use the GDB data even if SUPPORT data were not collected after withdrawal. We need to know from the center what we are allowed to use per their IRB and consent for GDB vs. SUPPORT.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

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404-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 1:43 PM
To: Gantz, Marie
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT DATA LOCK DATE - OCTOBER 20

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Wednesday, October 14, 2009 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,

Should (b) (6) be removed from outcome information? This is the mother that withdrew consent and further data collection?

Ellen

Ellen Hale, RN, BS, CCRC

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Neonatal Research Network

Emory University School of Medicine

Department of Pediatrics - Division of Neonatology

Office: 404-778-1679

Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 9:04 AM
To: Hale, Ellen; Fiher, Neil; Rich, Wade; Duara, Shahnaz; Reubens, Linda; Everett, Thomas; Ruth; Phelps, Dale; Michael O'Shea; Nancy Peters; (Luc.Brion@UTSouthwestern.edu); (tonis@uiim.edu); aar2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder; ((Bradley.yoder@hsc.utah.edu)); Brenda Poindexter; Carlo Waldemar (E-mail); cotreldj0@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz, Richard (E-mail); Ivan Frantz; ((ifrantz@tuftsmedicalcenter.org)); Kennedy, Kathleen A; Krisi Watterberg; Kurt Schibler; (Kurt.schibler@cchmc.org); Michelle Walsh; Mickey Caplan; Ohl, William (E-mail); Pablo Sanchez; Poole, Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson, David (E-mail); Barbara Stoll; Tyson, Jon (E-mail); VanMeurs, Krisa; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky Bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy-grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Cunningham, Meg; Auman, Jeanette O.
Subject: SUPPORT DATA LOCK DATE - OCTOBER 20

Hi,

REMINDER: SUPPORT Dataset for acute outcomes will be LOCKED following DMS transmission on October 20

Please insure that you have all of your queries and edits answered!

Thanks for all the help on this trial.

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Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
6100 Executive Blvd., Room 4B03

MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
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barbara_stoll@oz.ped.emory.edu

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20
Date: Wednesday, October 14, 2009 2:46:03 PM
Attachments: SUPPORT infants missing ROP - Center 9 02OCT09.rtf

---

This infant was withdrawn on DOL 11, so we have no eye exams entered on the SUPP10 and the ROP outcome is missing. Missing outcome reminders have not been generated for the infant because of the withdrawal, but they were on the comprehensive list of infants with missing ROP that went out two weeks ago (see attached).
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 2:35 PM
To: Gantz, Marie; Zaterka-Baxter, Kristin; Das, Abhik
Subject: FW: SUPPORT DATA LOCK DATE - OCTOBER 20

Can you check?

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Wednesday, October 14, 2009 2:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,
I was thinking we needed more ROP info on this baby but it is not on ROP list.
I think we are ok with ROP outcome.
Baby is on lost to follow up and we cannot locate. Call me at 404-778-1679.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 2:16 PM
To: Hale, Ellen; 'Gantz, Marie'; Ellen Hale; Barbara Stoll
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Please let us know if we can use GDB information on this child.

Thanks

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Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 14, 2009 2:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

We queried centers that had infants withdrawn from the study to find out whether we could use their data, but I do not see a response from Emory. Apparently, some centers can still use the GDB data even if SUPPORT data were not collected after withdrawal. We need to know from the center what we are allowed to use per their IRB and consent for GDB vs. SUPPORT.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 1:43 PM
To: Gantz, Marie
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT DATA LOCK DATE - OCTOBER 20

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From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Wednesday, October 14, 2009 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,

Should (b) (6) be removed from outcome information? This is the mother that withdrew consent and further data collection?

Ellen

Ellen Hale, RN, BS, CCRC

Neonatal Research Network

Emory University School of Medicine

Department of Pediatrics - Division of Neonatology

Office: 404-778-1679

Fax: 404-778-1467

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From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 9:04 AM
To: Hale, Ellen; Finer, Neil; Rich, Wade; 'Duara, Shahnaz'; 'Reubens, Linda'; Everett-Thomas, Ruth; 'Phelps, Dale'; 'Michael O`Shea'; 'Nancy Peters'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Barbara Stoll; Tyson Jon (E-mail); VanMeurs, Krisa; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; Cunningham, Meg; Auman, Jeanette O.
Subject: SUPPORT DATA LOCK DATE - OCTOBER 20

Hi,

REMINDER: SUPPORT Dataset for acute outcomes with be LOCKED following DMS transmission on October 20

Please insure that you have all of your queries and edits answered.

Thanks for all the help on this trial.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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6100 Executive Blvd., Room 4B03

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Infants Missing ROP Outcome at Center 9-Emory University

Network number	Date of Birth	Estimated PMA at 1st ROP exam (weeks)	Current estimated PMA (weeks)	Acute ROP status lost to FU at 55 week PMA	Final ROP status obtained at FU	FU window	FU status	Death date (if death after DC)	Infant was withdrawn from study
(b) (6)		36	249	Y	N	3=Closed	1=18 month FU visit completed	.	
		37	210	Y	N	3=Closed	4=Lost to FU	.	
		.	153			3=Closed	.	.	Y
		33	115			1=Not open yet	.	.	
		36	102			1=Not open yet	.	.	
		37	90			1=Not open yet	.	.	
		35	92			1=Not open yet	.	.	
		42	83			1=Not open yet	.	.	
		36	74			1=Not open yet	.	.	

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From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]; mganz@rti.org; airene@rti.org
Cc: Wally Carlo, M.D.
Subject: SUPPORT Queries Answered
Date: Wednesday, October 14, 2009 1:50:47 PM
Attachments: 1014102701.pdf

Here are the last of our queries--answered

Monica

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SUPPORT BPD Queries for Center 16-University of Alabama

1180

Center ID number=16=University of Alabama Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
Y	N	N	N	.	O2	RA	None	None	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	.	.

[redacted]

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query resolution Center notes
.	.	.	Off O2 @36wks per NG07 but on O2 per SUPP11. NG07 should record highest level of support for the day.		NG07 corrected to show O2

Center ID number=16=University of Alabama Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

[redacted] PHY01 complete

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC
Y	Y	N	N	.	O2	O2	None	None

PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA
.	.	N	.	.	.	.	.	.

SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query resolution Center notes
.	.	.	.	NG07-C is filled out but PHY01 is also expected for SUPPORT infants.		PHY01 Completed + entered

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

1044

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)			DC dates corrected → to be (b) (6)

Q125

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP08 infant had pneumothorax but it is not recorded on NG03.	SUPP08 AE (1a=Pneumothorax) entered for DOL 33 (b) (6) Please F5 if date is correct or edit date if not.	SUPP08 AE (7=Other) entered for DOL 33 (b) (6) Please F5 if date is correct or edit date if not.	AE deleted ~~due to date~~ > ~~14 days~~

1195

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Radiologist read IVH gr I & echogen in white matter – but never dx a gr 3-4. F5 Commented added to SUPP09

1233

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query resolution: Center notes
SUPP08 AE (2=Chest compressions or epinephrine in DR) entered for DOL 366 (b) (6). Please F5 if date is correct or edit date if not.			Δ date to (b) (6)

Different definitions on each form

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From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Shirley Cosby; Monica Collins
Cc: Gantz, Marie
Subject: RE: SUPPORT ROP queries Center 16 09OCT09
Date: Wednesday, October 14, 2009 1:01:07 PM

(b) (6) have not had a follow up eye exam to date per mother or pediatrician. However, when they come for their 18 month follow up visit, if an eye exam has been done since last contact, I'll correct the data entry.

(b) (6) has been referred to Indiana for the 18 month follow up. A home visit is being arranged by the follow up coordinator..

Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 4:06 PM
To: Wally Carlo, M.D.; Shirley Cosby; Vivien Phillips; Monica Collins
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 16 09OCT09

We have a few missing items and some queries for SUPPORT. Thanks for all your help!!!
Rose

16	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
16	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.
16	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.
16	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.
16	[redacted]	FU window has closed but NF05 and NF09a have not been completed.

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From: Zaterka-Baxter, Kristin
To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: RE: NICHD NRN SUPPORT TRIAL ROP Adjudication Process conference call
Date: Wednesday, October 14, 2009 11:39:05 AM

Dear all,

We have scheduled a conference call for **Friday, October 23, 2009 from 4:00 = 5:00PM (EST)** to discuss a process to adjudicate cases with unclear ROP outcome. Contacts below:

Call in number: 1-866-675-(b) (6)
Pass code (b) (6) (the "#" sign at the end is required)

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, October 12, 2009 2:48 PM
To: 'david.wallace@duke.edu'; 'Phelps, Dale'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dear all,

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: adjudication
Date: Wednesday, October 14, 2009 9:38:48 AM

Should I still schedule the meeting on 10/23 form 4 – 5 PM EST with Dale, Dr. Wallace, Marie, you and Abhik to discuss below or should we wait to have the 'formal' adjudication committee?
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 9:14 AM
To: Das, Abhik; Zaterka-Baxter, Kristin; Gantz, Marie; 'Phelps, Dale'
Subject: FW: adjudication

We will need an adjudication. We should have 3 ophthalmologists who are unaware of any study results look at the exams with indeterminate outcomes. We will need a table for each child constructed as follows:

Post menstrual age at exam (weeks)	Chronologic age at exam (in weeks)	Next several columns – data from SUPP10 for each exam				

For each infant, we will need birth weight and gestational age at birth – data must be de-identified (no dates).

I will look over the list that David Wallace sent and select folks for you to contact by the end of the day
Dale – do I have the necessary items in the table?
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 13, 2009 5:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: adjudication

If this were Inositol, I would yes absolutely yes.

Because SUPPORT is more complex I'm not so sure (with the 2x2 design, four outcome cells for analyses, 2 different primary outcomes).
However, I would favor having it in there. It relieves some uncertainties.

Dale

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 1:50 PM
To: Phelps, Dale; Abhik Das
Cc: Zaterka-Baxter, Kristin
Subject: RE: adjudication

Dale
Does this need to appear in the primary paper??
Thanks
rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 13, 2009 4:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Cc: Zaterka-Baxter, Kristin
Subject: RE: adjudication

I think it is worth the effort to do the adjudication. The results will be:
some who did have an adverse primary study outcome
many who had a good long term outcome, but we'll never know if they actually met criteria and resolved spontaneously
several that we'll be able to say almost certainly never met the criteria for the primary outcome data.

Given those three categories, it is very helpful to look at the primary outcome data and ask:
IF WE ASSUME
the probably bad were bad (first category)
and the probably good were good (last category)
and list a missing the middle category..... what does that do to the analysis?
the usual conclusion is 'no effect on conclusions'
this is very reassuring
it is reasonably conservative ... but ask Das and Wallace

IF further want to add in the 'middle category' in some fashion, I'd say worst case scenario, assume half good and half not... what does that do?

....
So if I'm a reviewer, I want to know that you examined the impact of these unknowns on your primary outcome. I don't want you to change your primary outcome, but I want you to do the work to tell me what the impact of those missed kids could have been. Would they have potentially changed your conclusions?
Usually when you do this you find that the answer is "No". (when there is pretty good follow up)

when the answer is squishy, it is usually because the follow up rates are quite bit lower, like 70-80%

Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 12:19 PM
To: Phelps, Dale
Cc: 'Zaterka-Baxter, Kristin'; 'Das, Abhik'
Subject: adjudication

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Dale
I have a practical pragmatic question –if the likely results for the adjudication are "unable to determine," is there a reason to expend the effort?

Thanks
Rose

Rosemary D. Higgins, MD
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From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; Johnson, Karen
Cc: Bell, Edward; Das, Abhik; Zaterka-Baxter, Kristin; Gantz, Marie
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20
Date: Wednesday, October 14, 2009 8:57:31 AM

Yes, that will be fine.

Karen, if you have a problem with that let me know and I can try to do the processing a bit later.

Thanks,
Jenny

Jeanette Auman
RTI International
Research Programmer/Analyst
(919) 237-1213
joa@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 14, 2009 8:56 AM
To: 'Johnson, Karen'; Auman, Jeanette O.
Cc: Bell, Edward; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

If the data are entered into the DMS on 10/20, we should be ok to include this infant Jenny – is this correct??
Thanks
Rose

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Tuesday, October 13, 2009 5:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bell, Edward
Subject: RE: SUPPORT DATA LOCK DATE - OCTOBER 20

Rose,
Well, as luck would have it, our "missing" subject's mom just called and he has a fever of 103, so they aren't coming tomorrow. We have him rescheduled for Tues, Oct 20 at 2:45. Can the lock wait until the end of the day, so that we can get his ROP outcomes in?
Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924

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pager (319) 356(b) (6), ask for pager(b) (6)

"Far and away the best prize that life offers is the chance to work hard at work worth doing." Theodore Roosevelt

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 8:03 AM
To: Finer, Neil; Rich, Wade; 'Duara, Shahnaz'; 'Reubens, Linda'; Everett-Thomas, Ruth; 'Phelps, Dale'; 'Michael O`Shea'; 'Nancy Peters'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa; (gloria.siaw@duke.edu); (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Elizabeth Billian; Ellen Hale; Georgia McDavid; Johnson, Karen; Kimberley Fisher; Leslie Wilson; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; Cunningham, Meg; Auman, Jeanette O.
Subject: SUPPORT DATA LOCK DATE - OCTOBER 20
Importance: High

Hi,

REMINDER: SUPPORT Dataset for acute outcomes with be LOCKED following DMS transmission on October 20

Please insure that you have all of your queries and edits answered.

Thanks for all the help on this trial.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Center for Developmental Biology and Perinatal Medicine
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From:	Bethany Ball
To:	Higgins, Rosemary (NIH/NICHD) [E]; Marie Gantz
Subject:	Re: SUPPORT ROP queries Center 15 09OCT09
Date:	Tuesday, October 13, 2009 8:21:15 PM
Attachments:	SUPPORT ROP ANSWERS Center 15 09OCT09.rtf ATT00001..htm SUPPORT ROP queries Center 15 09OCT09.doc ATT00002..htm

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Responses attached.

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SUPPORT ROP Queries for Center 15-Stanford University

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.							I reviewed the medical record and SUPP10 and found coding errors as well as missing exams. The SUPP10 has been completely re-done and re-keyed. BB

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 final ROP status was 2='severe ROP' but that is not reflected on the SUPP10.								Final ROP status on the NG03 changed to 1, determined favorable

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								Exam of (b) (6) has been keyed for exam #10. There is now one exam reported for (b) (6)

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated 07/01/08 highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated 07/08/08 highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated 07/17/08 highest ROP stage in lowest zone is > highest stage in any zone.						For the three exams in question, the highest stage in the lowest zone is 1. The SUPP10 has been corrected.

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SUPPORT ROP Queries for Center 15-Stanford University

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.							

Center ID number=15=Stanford University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 final ROP status was 2='severe ROP' but that is not reflected on the SUPP10.								

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated 07/01/08 highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated 07/08/08 highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated 07/17/08 highest ROP stage in lowest zone is > highest stage in any zone.						

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Finer SUPPORT Authorship ranking calculator (4).xls
Date: Tuesday, October 13, 2009 3:45:55 PM

Rose and all:

I have serious concerns about the importance of the % eligible as that metric provides little contribution to a trial. This is obvious from the results of this ranking. Some centers with minimal contribution rank higher that other that contributed more.

The carrot has to be given for the best reasons.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 1:07 PM
To: Wally Carlo, M.D.; 'Das, Abhik'
Cc: 'Zaterka-Baxter, Kristin'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Finer SUPPORT Authorship ranking calculator (4).xls

Hi,
Stephanie generated the author order list as per the NRN policy for ranking. 50% weight is given to absolute number recruited into a trial and 50% weight is given to % enrolled/% eligible. This may be viewed as "not fair." I brought it up on the hypothermia aEEG call today (same type of scenario with Dallas recruiting a large number of patients).

I want to discuss at the SC meeting - perhaps this should be revisited.

Rose

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]; Tyson, Jon E
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Author for SUPPORT FROM HOUSTON
Date: Tuesday, October 13, 2009 1:52:19 PM

Brenda did a lot of work on this study before she left. I took over then. I think it would be fair to include her as the site PI for the vent/CPAP arm paper and then I would be the site PI for the oximetry arm paper.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 11:05 AM
To: Tyson, Jon E; Kennedy, Kathleen A
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Author for SUPPORT FROM HOUSTON

I will tell you that two sites are having one author for the ventilation arm paper and another author for the oximetry arm paper.

Rose

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, October 13, 2009 11:53 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A
Subject: RE: Author for SUPPORT FROM HOUSTON

Brenda did a lot of work but up to Kathleen

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 10:46 AM
To: Kennedy, Kathleen A; Tyson, Jon E
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Author for SUPPORT FROM HOUSTON

Hi,

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We are working on the authorship for the SUPPORT main trial papers (one for vent arm, one for oximetry arm). We originally had Brenda Morris as the site PI for SUPPORT. Shall we list her on the paper or do you wish to designate a different investigator from UT Houston – let me know

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Huitema, Carolyn Petrie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORTcall10072009)_MGedits.doc
Date: Tuesday, October 13, 2009 1:29:05 PM
Attachments: SUPPORTcall10072009)_MGedits.doc

Hi Rose-

Marie had a chance to review these and wanted to run these by you before we posted.

Carolyn

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SUPPORT Subcommittee Call:
October 7, 2009

Participants: Drs. Finer, Carlo, Schibler, Higgins, Gantz, Laptook ,Das, Wallace. Ms. Zaterka-Baxter, Irene, Huitema, Newman.

Dr. Hintz's final protocol *Extended Follow-up at School Age (6½ to 7½ years) for the SUPPORT Neuroimaging and Neurodevelopmental Outcomes Cohort* was distributed to the subcommittee.

Support data lock is scheduled after the October 20th download. Dr. Gantz will continue to send Dr. Higgins weekly missing data reports to follow up with the sites.

SUPPORT Outcomes:

- The draft of the primary manuscript was sent to the subcommittee for review; BPD queries are still pending
  - The analysis of the CPAP vs. surfactant arm with pre-specified adjustments (GA, centers, multiples), showed no significant difference in the outcome of death or BPD by the physiologic definition. The outcome of death or BPD by oxygen at 36 wks was significant with a p-value just under .05 and favored CPAP.
  - In the small strata (24-25 wks), there was a significant increase in death in the surfactant arm (8%). However, overall there was no significant difference in death.
- The paper will be submitted to the NEJM

Comments:

- The traditional BPD definition is oxygen @ 36 weeks, however, 18 patients were on room air by CPAP or ventilation. The question is how to consider these patients with respect to BPD?
  - The 18 cases have not been evaluated in alternate analyses because Dr. Gantz did not want the outcome to influence alternate decisions.
  - Dr. Finer felt that the manuscript should report outcomes that are similar to other studies (e.g. COIN Trial) and to adhere to the definition of oxygen @ 36 weeks.
  - It is possible that these infants were on support in room air because of surgery.
  - There are only 3 cases where a baby was on CPAP or vent for a procedure and therefore not challenged.
  - The suggestion was to use a severity of BPD in Dr. Steven's Breathing Outcomes paper.

Pulse Oximetry

- Drs. Finer, Carlo, Das, Gantz and Wade Rich reviewed the pulse oximetry data together and found there was a significant increase in mortality in the low SpO2 arm by 4%. The low SpO2 arm had significantly less BPD by the definition of oxygen at 36 weeks (8% difference).
- The DSMC was tracking adverse events, including death, but the difference in death had not reached predefined significance levels for interim monitoring and no recommendations had been made.
- SUPPORT was the first trial to randomize infants to low and high arm of SpO2. There were no strong data in the literature prior to this study.
- Dr. Finer would like to get this manuscript published as soon as possible, to inform the community of the increase of deaths in the lower oxygen arm, including other studies currently randomizing infants to low SpO2 ranges. Suggest reporting ROP outcomes at Follow Up since there are currently several missing final ROP status data. The ROP data will not change the data related to death.

ROP

- The greatest difficulty is interpreting the ROP outcome due to missing final ROP status data.
  - About 50 patients had one exam in zone 3 but had not had a second consecutive exam with vessels in zone 3 and thus have not met the study criteria for final ROP status.

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- The ROP data is quite problematic. Dr. Finer suggested an ROP adjudication process. However, after consulting with Dr. Phelps it is highly unlikely that the data will be reclassified.
- Another issue is classifying those who have pending ROP exams but die after discharge. Dr. Finer stated that the outcome is defined as ROP or death before discharge. If the patient did not have ROP (did not reach threshold or have surgery) and did not die before discharge, that the patient will not be coded for either.
- Currently at 38 have FU window closed and no ROP outcome. Over 600 have been seen already.
- As seen in the data you could have Stage 2 ROP in zone 2 and end up with mature eyes; could also have threshold, no surgery and regressing eyes. Low sats babies spend about twice the amt of time in sats <85%.

Next Meeting

- The SUPPORT Subcommittee will meet 4:15- 5:00 pm Easter on October 28 at the Steering Committee Meeting – This meeting will be closed to Subcommittee members and DCC staff.

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call
Date: Tuesday, October 13, 2009 12:55:17 PM

Maybe we should discuss. It is difficult to schedule an ophthalmologist for a long call.
I'm not clear what the phone call should accomplish.
If it is planning the adjudication, that would be fine.
If it is the actual adjudication, I don't think we're ready.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 9:35 AM
To: Phelps, Dale
Subject: Fw: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Are you ok with this?
Shall we discuss?

From: Higgins, Rosemary (NIH/NICHD) [E]
To: 'dale_phelps@urmc.rochester.edu' <dale_phelps@urmc.rochester.edu>
Cc: 'kzaterka@rti.org' <kzaterka@rti.org>
Sent: Mon Oct 12 16:42:40 2009
Subject: Re: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dale
The primary outcome is death or ROP at status or 55 weeks as written in the protocol. Any child without an eye outcome is considered "missing.". The adjudication is for a secondary analysis of the data using assumptions based on the excams available. Let me know if this helps. I will be in the office tomorrow and can give you a call.

Thanks
Rose

From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Mon Oct 12 15:32:30 2009
Subject: FW: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Hi Rose,
I have concerns.

You only have one ophthalmologist. David Wallace can not be the only person in the group that has the clinical experience to make these judgements.
A phone call is a very inefficient use of time for these judgments . Especially with that many people, I don't think it will work well.
But maybe this is just a planning session?

David has identified 5 other ophthalmologists form our NRN centers that he thinks would be good. I will include his list. I have a partial draft letter, not sent, for them [attached] because I was waiting to talk to Abhik and Rose and Kris about how we would do this. Maybe you have decided already ???
Sharon Freedman here at Duke is excellent, and she knows plus disease. Which centers are in

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the Network?
David

Dale, From the list, I recommend 4 others (should make 6 if all agree):
Hutchinson
Hoffman
Neely
Yang
David

The Adjudication committee can not make a judgment about the primary outcome.
We have not established what the process will be, and that should be done before cases are examined.
I can help you a lot with how to present the data to the adjudication committee so that they can most efficiently absorb it.

Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, October 12, 2009 11:48 AM
To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dear all,

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road

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RTP, NC 27709 USA

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From: Hensman, Angelita
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Gantz, Marie"; Laptook, Abbot; Irene, Amanda
Subject: RE: SUPPORT ROP queries Center 14 09OCT09
Date: Tuesday, October 13, 2009 12:26:48 PM
Attachments: SUPPORT ROP queries Center 14 09OCT09.rtf

Resolution to ROP edits attached. I was not able to answer one (b) (6), I need to find out if "Early dilation" per exam under plus disease constitutes Plus disease".
Will send that in as soon as I get an answer.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 5:05 PM
To: Laptook, Abbot; Hensman, Angelita
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 14 09OCT09

Hi,
We are missing a few SUPPORT outcomes - The final date for data transmission is October 20.

thanks for all the help

Rose

14	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.

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SUPPORT ROP Queries for Center 14-Brown University

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								No mention of threshold on exam. Updated to threshold per edit/MOP criteria

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							Query 1 & 2 updated per edit/MOP criteria

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								Updated per edit. Threshold changed to 'yes" for left eye

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								Same exam entered twice due to updated forms. #6 exam deleted . #5 exam updated.

Center ID number=14=Brown University Network number=(b) (6) Date of Birt(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

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SUPPORT ROP Queries for Center 14-Brown University

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
				Query 1,2,3 & 4 changed to threshold ROP per edit/MOP criteria.

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							Query 1 & 2 changed to Threshold ROP per edit/MOP criteria

Center ID number=14=Brown University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	Per NG03 plus disease was diagnosed but that is not reflected on the SUPP10.							Query 1- #8 Right eye highest stage in lowest zone changed to 2. Query 2- "Early dilation" per exam under plus disease. Need to verify if this constitutes Plus disease.

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From: Grisby, Cathy (grisbyca)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP queries Center 11 09OCT09
Date: Tuesday, October 13, 2009 11:59:57 AM

Hi,
All of our SUPPORT edits have been addressed and will be transmitted today.
Cathy

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 5:00 PM
To: CHM-Schibler, Kurt (kurt.schibler); grisbyca@email.uc.edu
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 11 09OCT09

Hi,
attached are ROP queries. Please ensure they are answered. The last DMS transmission will be October 20.

Thanks for all the help
Rose

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call
Date: Tuesday, October 13, 2009 11:22:43 AM

Do I go ahead and set up this call? Dr. Wallace is available from 3:30 – 5:00 this day.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 12, 2009 4:43 PM
To: 'dale_phelps@urmc.rochester.edu'
Cc: Zaterka-Baxter, Kristin
Subject: Re: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Dale
The primary outcome is death or ROP at status or 55 weeks as written in the protocol. Any child without an eye outcome is considered "missing.". The adjudication is for a secondary analysis of the data using assumptions based on the excams available. Let me know if this helps. I will be in the office tomorrow and can give you a call.

Thanks
Rose

From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Mon Oct 12 15:32:30 2009
Subject: FW: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

Hi Rose,
I have concerns.

You only have one ophthalmologist. David Wallace can not be the only person in the group that has the clinical experience to make these judgements.
A phone call is a very inefficient use of time for these judgments . Especially with that many people, I don't think it will work well.
But maybe this is just a planning session?

David has identified 5 other ophthalmologists form our NRN centers that he thinks would be good. I will include his list. I have a partial draft letter, not sent, for them [attached] because I was waiting to talk to Abhik and Rose and Kris about how we would do this. Maybe you have decided already ???
Sharon Freedman here at Duke is excellent, and she knows plus disease. Which centers are in the Network?
David

Dale, From the list, I recommend 4 others (should make 6 if all agree):
Hutchinson
Hoffman
Neely
Yang
David

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We have not established what the process will be, and that should be done before cases are examined.
I can help you a lot with how to present the data to the adjudication committee so that they can most efficiently absorb it.

Dale

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, October 12, 2009 11:48 AM
To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
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Please let me know if you are willing and available this date and time.
Thanks,
Kris

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP queries Center 24 09OCT09
Date: Tuesday, October 13, 2009 9:14:36 AM

Thanks!

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
[illegible]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 9:14 AM
To: Gantz, Marie
Subject: FW: SUPPORT ROP queries Center 24 09OCT09

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Monday, October 12, 2009 2:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT ROP queries Center 24 09OCT09

We have corrected all the queries. Corrections will be transmitted tomorrow. Your query form with resolutions is attached. Our missing outcome family is supposed to come on Wednesday. Keep your fingers crossed!
Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (319) 356(b) (6) ask for page(b) (6)

"Far and away the best prize that life offers is the chance to work hard at work worth doing." Theodore Roosevelt

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 4:13 PM
To: Bell, Edward; Johnson, Karen
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 24 09OCT09

We have a few queries from SUPPORT (and one missing outcome).

thanks
rose

24	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP queries Center 24 09OCT09
Date: Tuesday, October 13, 2009 9:13:20 AM

Hi Rose,

Would you mind forwarding the document with the resolution of the queries? Thanks!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
301-514-8255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 13, 2009 8:54 AM
To: 'Johnson, Karen'; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT ROP queries Center 24 09OCT09

AWESOME!!
ROSE

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Monday, October 12, 2009 2:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT ROP queries Center 24 09OCT09

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: FW: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call
Date: Monday, October 12, 2009 3:32:36 PM
Attachments: Dear ophthalmologist.doc

Hi Rose,
I have concerns.

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A phone call is a very inefficient use of time for these judgments . Especially with that many people, I don't think it will work well.

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David

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Hoffman
Neely
Yang

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Dale

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Sent: Monday, October 12, 2009 11:48 AM
To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call

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Please let me know if you are willing and available this date and time.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
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RTP, NC 27709 USA

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Dear ...

Dr. David Wallace is helping us perform a review of ROP outcomes from a Randomized Controlled Trial conducted by the NICHD Neonatal Research Network. He has recommended you from the list of participating ophthalmologists at the 20 centers. We would like to invite you help us in this review.

The Study:

In a randomized study of ventilator practices and double-masked administration of two different levels of oxygen saturation, extremely preterm infants have been followed for the primary outcomes of ROP and chronic lung disease.

The Issue:

While most infants have had a final ROP outcome determined, some are in limbo. (failed to return for follow up, expired, missed exams with late follow up, etc.) The primary outcome is missing for these infants. However, a secondary outcome is useful for secondary analyses in such cases. These secondary analyses help to support the primary analysis of the trial, or determine the limitations of the analysis if they contradict the primary outcomes. They are very useful.

Your Role:

You would be asked to assign each case to one of the three outcomes:

1) Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye
2) Probably did meet criteria for ROP intervention in at least one eye
3) There is no way to know if ROP criteria may have been met

How it would work:

For each case, a summary of all ROP examinations along with basic demographic data and follow up ophthalmic data would be provided to you and the other reviewers. You would not know which group the infant was assigned to. You would not know in which center the infant was cared for.

You would score each case, not discussing it with anyone else.

Your scores would be returned to the Data Coordinating Center.

If there was consensus on a case, the consensus secondary outcome would be assigned.

If there was disagreement, depending on the number of disputed outcomes, there would be a conference call or in-person meeting to reach resolution.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: NEOProm meta analysis of oximetry trials
Date: Monday, October 12, 2009 3:30:42 PM

Infants will be linked to specific centers (and possibly to their siblings), but centers will be anonymized.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, October 10, 2009 7:55 AM
To: 'Roger.Faix@hsc.utah.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik; Gantz, Marie
Subject: Re: NEOProm meta analysis of oximetry trials

Good point. We will check it out.

From: Roger Faix <Roger.Faix@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Oct 09 23:41:52 2009
Subject: RE: NEOProm meta analysis of oximetry trials

Hi Rose!

Our site had no quads, although we did have twins and triplets. Unless multiples are somehow linked with a specific non-anonymized study site, it seems that subject anonymity should be preserved (at least for our enrollees) since 17 sites are involved. If there is no linkage of the data with our specific site, we do not anticipate having a problem.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 10:53 AM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Bradley Yoder; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,
Lisa Askie, who is leading the prospective meta analysis of the oximetry trials for which we are participating from the SUPPORT Trial is asking for birth order and sibling match to be included in the final data set. We do have information on birth order and sibling match in our data; however, there is a question of whether we can share that information due to privacy issues. For example,

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if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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To: david.wallace@duke.edu; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Auman, Jeanette O.
Subject: NICHD NRN SUPPORT TRIAL ROP data adjudication conference call
Date: Monday, October 12, 2009 2:48:15 PM
Attachments: SUPPORTManual20071015.doc

Dear all,

We will have the NICHD NRN SUPPORT Trial data lock on 10/20/09 and would like to ask that you be part of an adjudication committee to determine acute final ROP status (if possible) for cases that are not straight forward. We would like to have this conference call on **Friday, October 23, 2009 from 3:00 = 5:00PM (EST).** We would be sending the data for case reviews on 10/22/09. Currently, there are about 50 cases where the infant had one exam in zone 3 (instead of the two consecutive exams required to meet our final status requirement) and about 50 who only had exams in zone 2. The study subcommittee may determine these later cases are classified as undetermined per the study manual definition but after data lock we will have a better idea of cases needing review. I have attached the study manual for reference.

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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

NICHD Neonatal Research Network

Final

Manual of Operations

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Chapter 1

Overview and Trial Design

1.1 Introduction

This manual provides detailed instructions for study procedures related to The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Study): The manual is meant to serve as a reference guide for study staff including investigators, coordinators, technicians, and data managers. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the protocol dated August 28, 2004.

1.2 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (≤ 1 hour) surfactant and mechanical ventilation.
2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

The oxygen saturation monitoring portion of this study will be designed to parallel the planned POST-ROP trial, a multi-center, multinational prospective trial to evaluate different SpO2 levels from birth. The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices will be developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95% (Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

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Please refer to **Section 8.2** of the Protocol for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

1.4 Primary Hypothesis

1) We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2) We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

1.5 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD

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- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

1.6 Summary of Data Forms

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix A.

Screening Log (SUPP01)
A Screening Log (SUPP01) is provided to facilitate the tracking of infants with gestational age 27 6/7 weeks or less for whom a decision has been made to provide full resuscitation as necessary in the Network centers.

Eligibility Form (SUPP02)
This form will be completed for all inborn infants with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimates and who are to receive full resuscitation as necessary.

Delivery Room Form (SUPP03)
Data for this form will be collected in the delivery room and will be completed on all infants.

NICU Admission and Procedures Form (SUPP04)
This form is to be completed on all infants enrolled in the study upon admission to the NICU.

NICU Admission and Procedures Form (SUPP04a- Surfactant Doses)
This form is to be completed if more that 4 surfactant doses are given between the first dose in the NICU and day 14 of study.

Safety Monitoring Form (SUPP05)
This form is to be completed each day starting with Study day 1 until Study day 14 or outcome status, whichever comes first.

Safety Monitoring Form (SUPP05A)
This form is to be completed each time an intubation/extubation occurs after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

Protocol Deviation Form (SUPP06)
This form will be completed for all randomized patients whenever a protocol deviation/violation is encountered.

Reintubation Form (SUPP07)
This form will be completed for all intubation/extubations after 14 days.

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Adverse Event Form (SUPP08)
This form will be completed for the adverse events, as specified in the protocol, occurring during the initial 14 days of life.

MedWatch Form (SUPP08A)
This form is to be completed in the event of a serious adverse event. It should be faxed to Ken Poole (919) 485-7762 and Rosemary Higgins (301) 496-3790 within 24 hours or the next working day.

Outcome Status Form (SUPP09)
This form will be completed when the infant is discharged home, transferred, if hospitalized at 120 days, death or withdrawn (whichever comes first).

ROP Outcomes and Tracking Summary (SUPP10)
The form will be used to record data for each eye examination (in or outpatient) until both eyes are acute/final.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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Chapter 2

Administration

2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

2.2 SUPPORT Trial Subcommittee

The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, RN

Wade Rich, RRT

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2.3 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center and the principal investigator is located in the second column.

PARTICIPATING CENTERS	NRN PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Pablo Sanchez	Pablo Sanchez
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Seetha Shankaran, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Kurt Schibler, MD	Vivek Narendran, MD
Indiana University (12)	Brenda Poindexter, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	Krisa Van Meurs, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Kathleen Kennedy MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	C. Michael Cotten, MD
University of California-San Diego (22)	Neil Finer, MD	Neil Finer, MD
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, MD

2.4 Responsibilities of the Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, and a small number of unmasked personnel who will provide 24 hour coverage to monitor study equipment.. The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

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The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Presenting an in-service to the appropriate nursing and ancillary staff detailing the study protocol
- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network microcomputer
- Controlling access to the network microcomputer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Achieving and maintaining fluency with the procedures for obtaining the treatment group assignment from the data center
- reporting deviations to the data center within 24 hours of occurrence

2.5 Responsibilities of the Data Coordinating Center

The DCC is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing, printing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study.

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2.6 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs including pharmacies, study drug supply, and other special requirements of the study.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

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Chapter 3

Screening, Eligibility, Consent

3.1 Study Population

Study subjects are inborn infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants born during a time when the research apparatus/study personnel are not available

3.4 Informed Consent

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. As discussed in Section 4.1, randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

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Chapter 4

Randomization

4.1 Randomization Procedures

Randomization will be stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and will occur prior to delivery for consented deliveries. The randomizations will be performed by **utilizing specially prepared envelopes**. The Data Center will prepare brown sealed envelopes which will contain the identity of the treatment combination to be assigned the infants enrolled into the study. **Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial.** One envelope will correspond to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery will receive the same treatment combination.

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group. These should be kept in separate boxes or drawers with the group clearly indicated **(this will be noted on the label on the front of the envelope).** The envelopes will be sequentially numbered with a randomization number on the outside of the envelope so they can be selected in the order of use to maintain a balancing of the treatment assignments. These envelopes are to be stored in a secure place in or near the delivery for quick accessibility.

The envelope should be selected, from the appropriate group, and opened at the time of delivery by a study staff member only when the delivery is imminent. Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue or Orange**
  OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue or Orange.**

The **Blue/Orange codes** will designate an assignment to either the **Low (85% - 89%)** or **High (91% - 95%)** SpO2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).
Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be

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identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know".** Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO2) are available to accommodate the delivery.

Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.

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Chapter 5

Study Interventions

5.1 Study Intervention A

5.1.1 Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines. Once stabilized:

- All **Control infants** in both strata will receive prophylactic/early surfactant (within 1 hour of age).
- All **Treatment infants** will be placed on CPAP/PEEP following stabilization, and will be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by **Study Oximeter Assignment** will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

Treatment Groups

5.1.2 CPAP Group: Early Extubation and CPAP – Both Strata

5.1.3 Delivery Room Management

1) FiO2:
Standard of care

2) CPAP:
CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. High flow nasal cannula (e.g. Vapotherm) may not be used as the primary mode of therapy for infants randomized to Early CPAP in the first 14 days.

3) Intubation:
Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth. Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

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The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

5.1.4. NICU Management

These infants will be managed on nasal CPAP and intubation is never required by protocol. They ***MAY*** be intubated if they meet ***ANY*** of the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant.

1. **Intubation:**
   - An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
   - A $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas
   - Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

2. **Extubation:**

An intubated CPAP-Treatment infant ***MUST*** have extubation attempted within 24 hours if ***ALL*** of the following criteria are met and documented on a single blood gas:

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

*Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation (**on the SUPP06 Form**) unless extenuating circumstances are noted (e.g. PIE, airleak).*

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3. Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.

Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants ***MAY*** be reintubated if they meet ***ANY*** of the following:

4. Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour
- A $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) on a single blood gas
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. Note that clinically defined shock is an accepted indication for intubation.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

5. D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. May be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

6. Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant. Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

5.1.5 Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

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5.1.6 Control Group- Prophylactic/Early Surfactant and Ventilation

5.1.7 Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

5.1.8 NICU Management:

1. Extubation:

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas:

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤.35 with a SpO2 ≥ 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation ***(on Form SUPP06)*** *unless extenuating circumstances are noted.*

2. Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

3. Reintubation:

- Control Infants may be reintubated using Standard of Care. Any subsequent extubations will also follow standard practice.

5.1.9 Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants

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as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

5.2 Study Intervention B

5.2.1 Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) as described below will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. As an added safety feature, the POs used in this trial will gradually revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

5.2.2 Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen.

The study pulse oximeters will be applied to the infant within two hours following NICU admission. The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

5.2.3 High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen.

The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until discharge 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% to 96% for both groups. All values outside of alarm limits will be unaltered values.

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The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table 1 below.

Table 1

Output and Actual SpO2 Targets and Alarms

Group	Display Target	Actual Target	Alarm Values
Low SpO2 range	88-92%	85-89%	<85 and >95%
High SpO2 range	88-92%	91-95%	<85 and >95%

Every 30 days until 36 weeks PCA, or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses to determine that were are within the desired ranges. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without loosing significant data). These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

See Flow of Study Intervention on page 5.7:

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Flow of Study Intervention

	Early Extubation and CPAP	Prophylactic/Early Surfactant and Ventilation
Delivery Room Management:	• Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. • Transport on CPAP **If intubated for resuscitation** • Give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	• Intubate and give surfactant within 1 hour of age • Transport with PPV according to SOC
Upon NICU Admission:	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria:	**May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria:** **Standard of Care**
Extubation Criteria:	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 ≥ 88% with an FiO2 ≤ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 ≤ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surfactant Doses:	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation:	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.	
CPAP D/C:	In room air for at least 1 hour	
CPAP Resumption:	At any time	
Duration of Intervention:	14 Days	14 Days

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5.3 Delivery of Interventions

5.3.1 CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator a neonatal ventilator, or an equivalent device that is currently used by the site for the delivery of CPAP.

5.3.2 Use of Nasal SIMV

For uniformity nasal SIMV may be used in place of CPAP ***only following extubation*** for both Treatment and Control infants.

5.3.3 Use of Caffeine

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.

5.3.4 Surfactant Type

All centers are asked to follow current unit practice in determining the type of surfactant utilized and manufacturers' recommendations for re-dosing intervals.

At least one dose of surfactant **must** be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.

5.3.5 Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

5.3.6 Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window.

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5.4 Protocol Violations

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of an Early Extubation and CPAP infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for an Early Extubation and CPAP infant requiring `supplemental oxygen
3. Intubation and surfactant administration of an Early Extubation and CPAP infant without meeting stated protocol criteria.
4. Failure to extubate an Early Extubation and CPAP infant who fulfills all the extubation criteria.
5. Extubation of a Prophylactic/Early Surfactant and Ventilation infant who does not meet any of the extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations. The Protocol Violation/Deviation Form (SUPP06) should be completed each time a violation/deviation is encountered.

5.5 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades III-IV, Papile)
4. Pulmonary hemorrhage
5. Nasal breakdown requiring discontinuation of nasal prongs
6. Death

These outcomes will be evaluated on a monthly basis by RTI using sequential analysis boundaries, and if the incidence of any of these outcomes differs among the treatment arms of the study this information will be provided to the DSMC for immediate evaluation and consideration of termination of the study or treatment arm. The SUPPO8 (Medwatch Form) should be completed in the event of a serious adverse event. It should be faxed to RTI (919) 485-7762 and Rosemary Higgins (301) 496-3790 within 24 hours or the next working day.

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Chapter 6

Screening Log

6.1 Instructions for completing the Screening Log (SUPP01)

Each center will implement an effective and efficient screening procedure to identify all potential study subjects. A Screening Log (SUPP01) is provided to facilitate the tracking of infants with gestational age 27 weeks or less for whom a decision has been made to provide full resuscitation as necessary. The following information is used to identify each infant and is placed on the screening log.

Center Number
Each study center has been assigned a Network center number.

Site
Centers with more than one participating hospital also have a site code (A, B, C or 1, 2, 3).

THE FOLLOWING INFORMATION WILL BE FILLED OUT WHEN THE MOTHER IS FIRST SCREENED:

Mother's Last Name
The last name of the mother who is being screened should be written on this log. This confidential information is recorded for the convenience of the center and must not be submitted to the DCC.

Mother's Hospital Number
The hospital number of the mother should be recorded. This confidential information is recorded for the convenience of the center and must not be submitted to the DCC.

Gestational Age
Record the actual gestational age in weeks and days when the mother is identified.

Last Date Eligible
Record the date this mother will reach 27 6/7 completed weeks. This will be the date when her infant would no longer be eligible for enrollment in this study. This will be used as a guide to track a mother who may be at risk for premature delivery but who may not deliver within the window of the study.

Consent
Record 'Y' or 'N' if consent has been obtained. If consent is obtained this pregnancy/infant birth will be followed to determine eligibility.

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THE FOLLOWING INFORMATION WILL BE FILLED OUT ON THOSE PATIENTS WHO HAVE GIVEN CONSENT WHEN THE INFANT IS BORN WITHIN THE ELIGIBLE WINDOW:

Date of Birth

Enrolled in Study
Record 'Y' or 'N' if infant was enrolled in this study. This will ensure that all potential infant outcomes were identified (including but not limited to: enrolled in the study, gestational age at birth >28 weeks, died in delivery room).

Network Number

Record the Network number of any infant enrolled in the study.

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Chapter 7

Eligibility Form

7.1 Instructions for completing the Eligibility Form (SUPP02)

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, Birth Number and Mother's Initials **(optional).**

7.1.1 Form Section A: Eligibility Criteria

If any criteria are not met, the infant is ineligible.

1. Inborn infant with a gestational age of 24 weeks 0 days to 27 6/7th completed weeks by best obstetrical estimate?
Code yes if the infant was 27 completed weeks or less by best obstetrical estimate or by appropriate clinical examination.

2. Infants who will receive full resuscitation as necessary?
Code yes if the infant will require full resuscitation as necessary

3. Infant who does not have know major congenital malformations?
Code yes if the infant does not have known major congenital malformations.

If any of the above questions are answered No the infant is NOT eligible.

7.1.2 Form Section B: Exclusion Criteria

1. The infant was born during a time when the research apparatus/study personnel are not available?
Code yes if there was no apparatus/study personnel available.
If Yes, indicate the reason:
1= Equipment not available
2= Personnel not available

7.2 Form Section C: Consent

Sample consent forms for this study are included in Appendices D and E.
Consent status:

Answer this question with one of the following codes, according to the following definitions:

0 = Not Eligible
Code '0' if one or more of the eligibility criteria questions are answered "No". If the infant is ineligible, regardless of whether consent was granted or not, this code should be used.

1 = Consent Granted
Code '1' if parenteral/guardian consent is obtained.

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2 = Parent Unavailable
Code '2' if the parent or legal guardian is unavailable throughout the eligibility period

3 = Parent Refused Consent
Code '3' if a parent or legal guardian refuses consent.

4 = Consent Not Requested
Code '4' if consent for this study was not requested. Language or social problems as well as enrollment in conflicting trials should be recorded here.

5 = Physician Refused Consent
Code '5' if the infant was eligible for the study, but the attending physician refused to consider the baby for enrollment.

If the consent status is 3, 4, or 5, indicate the reason why consent was refused or not requested.

If the patient is eligible and consent is granted, but the patient is not randomized, indicate the reason why the eligible infant was not randomized into the study although consent from both parent/guardian and physician was obtained.

7.3 Form Section D: Randomization

An infant is eligible for randomization if all eligibility criteria are answered Yes in Section A. The infant is considered randomized at the time the randomization number is given.

1. **Was infant randomized into the study?** Record "Yes" if the infant was randomized into the study.
   If No, indicate the reason the infant was not randomized.
   If Yes,
   a. Date of Randomization- Enter the date on which the randomization envelope was opened to enroll the infant into the study. All dates for this study are recorded using the MM/DD/YYYY format.
   b. Time of Randomization- Enter the local time at which the envelope was opened to randomize the infant.
   c. Randomization Number-Enter the randomization Number. This number is recorded on the SUPP02 during the randomization. The randomization numbers are four digit numbers with a different set of numbers, stratified by gestational age, for each group. There will be a group with gestational age from 24 - 25 6/7 weeks and a group with gestational age 26 to 27 6/7 weeks. The groups for each Center will be as follows:

   24 - 25 6/7 weeks = 3001 - 3160
   26 - 27 6/7 weeks = 4001 – 4160

   d. Treatment Assignment:
   Enter 1= Early Extubation and CPAP or 2= Early Surfactant and Ventilation

   e. Oximeter Color Code
   Enter 1= Blue or 2=Orange

   All times for this study are recorded using the 24-hour clock format (00:00 to 23:59).

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Chapter 8

Delivery Form

8.1 Instructions for completing the Delivery Form (SUPP03)

8.2 Form Section A: Delivery Room Information

1. Date and time of Delivery

a. Date:

Record the date on which child was born (day begins at 00:00, ends at 23:59).

b. Time:

Use a 24-hour clock with midnight coded as 00:00.

2. Was CPAP initiated in the DR? An application of CPAP will be considered the fitting of a mask over the infant's airway without intermittent positive pressure breaths or the placement of nasal prongs.

Record 'Y' if CPAP was initiated in the DR

a. If Yes, time of CPAP initiation

Use the 24-hour clock with midnight coded as 00:00

b. Device: Record Device.

1= Neopuff
2= Ventilator
3=Anesthesia Bag
4= Bubble
9 =Other

If Device is 5, specify the type.

3. Was positive pressure ventilation (PPV) initiated in the DR? PPV is defined as the administration of intermittent positive pressure breaths using either a mask or endotracheal tube.

4. Was positive end-expiratory pressure (PEEP) used in the DR?

Record 'Y' if PEEP was used in the DR

a. Maximum PEEP:

Record the maximum PEEP level as cm/H_20

5. Was intubation attempted in the DR?

a. **If Yes, was the intubation successful?**

Code Yes if the intubation was successful.

6. Indication for intubation

Record the indication for intubation;

1= Surfactant administration

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2= Resuscitation
3 = Other (specify)
4 = As required by randomization assignment
Code 4 will be used to indicate that the infant was intubated because of the protocol assignment of Early Surfactant.

If for (2) Resuscitation
a. Low HR? Record Yes if the infant was resuscitated because of low HR.
b. Poor color? Record Yes if the infant was resuscitated because of poor color.
c. Apnea? Record Yes if the infant was resuscitated because of apnea.
d. Other? Record Yes if the infant was resuscitated for any other reason and specify the reason.
If for (3) Other, specify the indication for intubation.

7. Did the infant receive surfactant in the delivery room?
Record 'Y' if the infant received surfactant in the DR.
If Yes, Date and time of surfactant administration
a. Date: Record the date of surfactant administration using the mm/dd/yyyy format.
b. Time: Record the time of surfactant administration using the 24-hour clock with midnight coded as 00:00.

c. Type: Record the type of surfactant given
1= Infasurf
2= Curosurf
3= Survanta
4= Exosurf
5= Other, specify the type.

8. Was active resuscitation required? Record 'Y' if active resuscitation was required which would include bag and mask ventilation and/or intubation in the delivery room.
If Yes,
a. Chest compressions?
Record 'Y' for external pressure over central chest to contract heart.
If Yes,
1. Duration: Record the duration of chest compressions in minutes.
b. Epinephrine?
Record 'Y' if Epinephrine was provided to the infant at the time of birth irrespective of route (intratracheal or intravenous)
1. Number of doses: Record the number of doses the infant received.

9. Status following resuscitation:
Record 'the status of the infant at delivery.
1= Admitted to the NICU for further care
2= Infant died

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Chapter 9

Admission to NICU Form

9.1 Instructions for completing the Admission to NICU Form (SUPP04)

The purpose of this form is to determine if the study interventions are applied as per the protocol

9.2 Section A. NICU Admission

1. Date and time of admission to the NICU:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59

b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00.

2. Respiratory support on admission to the NICU:

Record the respiratory support as:
1= HVF
2= CV
3= Nasal SIMV
4= CPAP
5= NC
6= Hood
7= No Support

3. SaO_2

Record the infant's SaO_2 on admission to the NICU.

4. FIO_2

Record the infant's FiO_2 on admission to the NICU.

5. Was a blood gas done after admission to the NICU?

If Yes, Record the first blood gas obtained following the NICU admission:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59

b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00

c. Source: Record the source of the first blood gas
1= Arterial
2=Venous
3= Capillary

Record the results of the first blood gas.

d. pH:

e. pCO_2:

f. pO_2:

g. FiO_2:

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6. Date and time the study oximeter was placed on this infant.
Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00
c. Serial Number: Record the serial number that is pre-labeled on the oximeter.

9.3 Section B. NICU Procedures

1. Was the infant intubated for the first time after admission to the NICU within the first 14 days?

If Yes, Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00

c. Indication for intubation:

1. Surfactant?
2. FIO_2 > .50 to maintain $Sa0_2$ ≥88%?
3. $PaC0_2$ >65 on single blood gas?
4. Apnea requiring bag and mask ventilation?
5. If No to all above, state reason:

Record reason:
1= Hemodynamic instability
2= Clinical shock/sepsis
3= Other reason, If other, specify other reason.

2. Was a blood gas done within 30 minutes prior to intubation?

Note: Complete this question only if question B.1 = YES

If Yes, Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00
c. Source: Record the source of the first blood gas
1= Arterial
2=Venous
3= Capillary

Record the results of the first blood gas.
d. pH:
e. $pC0_2$:
f. pO_2:
g. FiO_2:

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3. Was Surfactant given in the NICU?
If Yes, Record the following for each dose: If more than 4 doses given see form SUPP04a

a. Date: Record the date the infant received the first dose of surfactant in the NICU and for the first 14 days. Day begins at 00:00, ends at 23:59
b. Time: Record the time the infant received the first dose of surfactant in the NICU using using the 24-hour clock with midnight coded as 00:00
c. Type: Record the type:
   1= Infasurf
   2= Curosurf
   3= Survanta
   4= Exosurf
   5 = Other, If other, specify type.

Note: If more than 4 doses were given, record each additional dose on form Supp04a.

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Chapter 10

Safety Monitoring Form
SUPP05 SUPP05A SUPP05B

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

1. Study Day: Enter the day this form is being completed.

2. Date: Enter the date that corresponds to the Study Day.

3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured
Record the actual time that the FiO2 was obtained based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

f. FiO_2
Record the FiO_2 at the scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

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h. Mode of Support
Record the respiratory support as:
1 = HFV
2 = CV
3 = Nasal SIMV
4 = CPAP
5 = NC
6 = Hood
7 = No Support
8 = Infant temporarily out of unit
9 = No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual time that the blood samples were collected based on a 24-hour clock. This time should be closest to 08:00, 16:00 or 23:59. If one blood gas qualifies as closest to two scheduled times (e.g. 23:59 and 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one.

c. pH
Record the acid base status of the blood.
d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

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g. Source:
Record the source of the blood gas
1= Arterial
2= Venous
3= Capillary

h. Mode of Support
Record the respiratory support as:
1 = HFV
2= CV
3 = Nasal SIMV
4 = CPAP
5 = NC
6 = Hood
7 = No Support
8 = Infant temporarily out of unit
9 = No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

5. Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine. The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

6. Was the infant intubated or extubated on this day?
If Yes, Complete the SUPP05A

10.3 Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 6 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete a new report for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

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Report Number
Consecutively number each event as reported on the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

3 Was the infant intubated on this day?
Record Yes if the infant was intubated on this day.
If Yes,
a. Record the time of intubation:
b. Record the following information prior to intubation:

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation
4. Apnea? Record Yes if the infant had Apnea on this day.
5. Sepsis/R/O Sepsis? Record Yes if the infant had Sepsis/R./O Sepsis on this day.
6. Hemodynamic instability? Record Yes if the infant had hemodynamic instability on this day.
7. Clinically significant PDA? Record Yes if the infant had clinically significant PDA on this day.
8. Other (specify). Record Yes if the infant had other conditions this day. Specify these.

4. Was the infant extubated on this day?
Record Yes if the infant was extubated on this day.

If Yes,
a. Record the time of intubation:

b. Type of extubation:
1= Planned
2= Accidental

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c. Record the following prior to extubation

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. Episode Number
Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. Date Oximeter Replaced
Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. Time Oximeter Replaced
Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. Replacement Oximeter Serial Number
Record the six digit serial number of the replacement oximeter used.

e. Replacement Oximeter Color Code
Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

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Chapter 11

Protocol Deviation Form

11. 1 Introduction

The purpose of the protocol deviation form is to facilitate the accurate documentation of the facts and circumstances surrounding a deviation from or violation of the protocol. This form should be completed for all randomized patients whenever a protocol deviation is encountered by study personnel. ***This form will be keyed at the sites.***

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

11.2 Instructions for completing the Protocol Violation Report (SUPP06)

1. Date of Protocol Deviation:
Record the date the deviation was first encountered using the mm/dd/yyyy format.

2. Type of Protocol Deviation:
Record the type of protocol deviation:
1= Infant intubated without meeting study criteria
2= CPAP not initiated if required by the protocol
3= Surfactant not given in the first hour
4= Mechanical ventilation initiated for other than study criteria
5= NSIMV initiated in infant not previously intubated
6= Extubation (exclude unplanned extubation) for other than study criteria
7= Failure to extubate CPAP infant if all criteria are met
8= Infant received incorrect treatment assignment
If protocol deviation =8, indicate the treatment arm.
1= Ventilator strategy
2= Oximetry strategy
3= Both
9= Oximeter not started within 2 hours.
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
99= Other: Specify type of protocol deviation

3. Circumstances of the protocol deviation/violation:
Briefly describe the circumstances that led to the protocol deviation/violation. In particular, if there were medical reasons for deviating from/violating the protocol, describe them.

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4. Additional comments:
Record any additional comments or information here such as steps taken to prevent recurrence of the deviation/violation.

5. Name of the person reporting the deviation/violation:
The name of the individual making the report should be recorded here.

6. Date Protocol Deviation Form is completed:
Record the date this form was completed.

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Chapter 12

Reintubation Form

12.1 Introduction

The purpose of this form is to document all reintubations after day 14 for the duration of hospital stay.

12.1.1 Instructions for completing the Reintubation Form (SUPP07)

Complete this form for every reintubation and subsequent extubation after 14 days for the duration of hospital stay until status.

a. Event
Enter event code as:
1= Reintubation
2= Extubation

b. Date of event:
Enter the date of the event using the mm/dd/yyyy format.

c. Reasons for reintubation:
1 = Apnea / hypoventilation
2 = Increased respiratory effort
3 = Sepsis/Possible sepsis
4 = Atelectasis
5 = Elective procedures
6 = Upper airway abnormality
7= Self/Unplanned
8 = Other reasons

Record the code(s) corresponding to the reason(s) for the reintubation as recorded from the chart. There may be a maximum of three reasons recorded.

If code =8 other reasons, specify reason for reintubation if it is not listed.

d. Record FiO_2 and PCO_2 if available:
Record the FiO_2 and PCO_2, if within 6 hours prior to the event.

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Chapter 13

Serious Adverse Experience

13.1 Introduction

Serious and unanticipated adverse events may be anticipated in this vulnerable population. **Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:**

13.2 Adverse Event Form (SUPP08)

Complete this for any randomized infant who experienced one or more of the following adverse events during the initial 14 days of life Record a consecutive Report Number in the header for each form submitted. This form should be completed and keyed at the sites as soon as possible.

1. Air leak

a. Pnemothorax
Record 'Y' if pneumothorax is documented in the infant's chart. Pneumothorax is a collection of air in the pleural space where a lucency is identified in the pleural space with displacement of the lung away from the chest wall. Do not include a pneumothorax resulting from a thoracotomy during surgery (e.g. PDA ligation). Otherwise code 'N'

b. Pulmonary Interstitial Emphysema (PIE)
Record 'Y' if pulmonary interstitial emphysema (PIE) is documented in a radiographic report in the infant's chart. PIE is a radiographic and pathologic diagnosis made when air ruptures from alveoli or small airways into the perivascular tissues of the lung. This diagnosis will only be documented if from the radiographic reports. Do not include PIE documented in patient notes unless there is radiographic documentation to support this diagnosis. Otherwise code 'N'

c. Pneumopericardium
Record 'Y' if pneumopericardium is documented in the infant's chart. This documentation may be found in a radiographic report, echocardiogram report or patient progress notes. Pneumopericardium is an extrapulmonary collection of air in which the air completely surrounds the heart, including its inferior border. Otherwise code 'N'.

If coding 'Y' to question 1.a, b or c above, code most proximate mode of ventilatory support for each occurrence as follows:

1 = HFV
2= CV

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3 = Nasal SIMV
4 = CPAP
5= NC
6= Hood
7= No Support
8 = Infant temporarily out of unit
9= No Support all day and off Study oximeter

Record 'Date of Onset" and 'Attribution to SUPPORT study' for each occurrence.

2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[i]
4. Pulmonary Hemorrhage
5. Nasal breakdown requiring discontinuation of nasal prongs
6. Death
7. Other (specify) Specify if there were other adverse events.

13.3 Definition of a Serious Adverse Experience

1. An adverse experience is any undesirable experience associated with the use of a medical product in a patient.
2. Associated means that there is a reasonable possibility that the experience may have been caused by the drug.
3. Serious adverse experience means any experience that suggests a significant hazard, contraindication, side effect or precaution.
4. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Death
Submit a report if the patient's death is suspected as being a direct outcome of the adverse event.

Life Threatening
Submit a report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death
.
Examples are: pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow, resulting in excessive drug dosing.

Inpatient Hospitalization (initial or prolonged)
Submit a report if admission to the hospital or prolongation of a hospital stay results because of an adverse event. Examples are: anaphylaxis, pseudomembranous colitis, or bleeding causing or prolonging hospitalization.

Disability
Submit a report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or

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quality of life. Examples are: cerebrovascular accident due to drug-induced hypercoagulability, toxicity, peripheral neuropathy.

Requires Intervention to Prevent Permanent Impairment or Damage
Submit a report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient. Examples are: acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage, burns from radiation equipment requiring drug therapy, breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Adverse experiences will be reviewed by the Data Safety and Monitoring Committee.

13.4 Completing the MedWatch Form (SUPPO8A)

In the event of a patient death or unexpected serious adverse event not documented in the case report form, the PI must be notified right away. The attending physician should write a detailed description of the clinical events to include all the elements of the FDA 3500A (MedWatch) form (see Appendix **A**), the patient's date of birth, Network number, and whether the treatment was stopped. The description should be faxed to Dr. Rosemary Higgins at NICHD (301 496-3790) with a copy sent to Kris Zaterka-Baxter at the DCC (919 485-7762).

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Chapter 14

Outcome Status Form

14.1 Introduction

The purpose of this form is to document the final outcome status of the infant.

14.1.1 Instructions for completing the Outcome Status Form (SUPP09)

This form is to be completed when the infant is discharged to home, transferred, if hospitalized at 120 days, death or withdrawn (which ever comes first).

14.1.2 Section A - Infant Outcome

1. **Status of infant at time of completion of form:**

   - **Discharged to home**
     Record '1' if infant was discharged to home without returning in 7 days.
   - **Still in hospital at 120 days**
     Record '2' if infant is still in the hospital at 120 days.
   - **Transferred to another hospital**
     Record '3' if infant was transferred to another hospital without returning in 7 days.
   - **Transferred to chronic care facility**
     Record '4' if infant was transferred to a chronic care facility without returning in 7 days.
   - **Death**
     Record '5' if the infant died.
   - **Withdrawn form study**
     Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

2. **Date of status:**
   Give date at status.

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14.1.3 Section B - Neurologic

1. Did the infant have a head ultrasound between 4 - 21 days of age?
Code Yes if an ultrasound was performed between 4 - 21 days. Code No otherwise. If a cranial ultrasound is not done for standard of care, the study requires that at least one HUS be completed during this window.

If Yes,
a. Date of ultrasound:
Record the date of the head ultrasound obtained using the mm/dd/yyyy format. **Note**: If more than one head ultrasound is done between 4 - 21 days of age, record the date of the most severe.

If Yes,
b. Time of ultrasound:
Enter the time of the head ultrasound obtained using the 24 hour clock format (00:00-23:59).

c. Infarct?
Code Yes if an infarct was diagnosed by the local sonographer. Code No otherwise.

d. IVH?
Code Yes if evidence of intraventricular hemorrhage was observed on the head ultrasound. Code No otherwise.

If Yes,
1) IVH Grade:
Enter the severity of the intraventricular hemorrhage observed on the head ultrasound using the Papile scale:

Grade I: Code 1 if the echodensity/hemorrhage is confined to the germinal matrix/subependymal area.

Grade II: Code 2 if there is an echodensity/hemorrhage in the lateral ventricle(s) without distention.

Grade III: Code 3 if there is an echodensity/hemorrhage in the lateral ventricle(s) with distention.

Grade IV: Code 4 if there is an echodense lesion in the parenchyma.

e. PVL?
Code Yes if periventricular leukomalacia (increased echogenicity or cysts in periventricular region) was observed on the head ultrasound. Code No otherwise.

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14.1.4 Section C – Ophthalmology

1. Was an exam performed for Retinopathy of Prematurity (ROP)?
Review the medical record to determine if an examination was performed for ROP.
If Yes, complete the **SUPP10 Form** (ROP Outcomes And Tracking Summary).
If No, and the infant survived, complete the **SUPP10** (ROP) form based on subsequent exams (including back-transfer hospital and/or outpatient visits)

14.1.5 Section D – Postnatal Steroid Use

1. Did the infant receive postnatal steroids after the first 21 days of life?
If Yes, record the information on number of courses, start date, stop date, drug administered and total dose administered during the course in mg/kg. If No, the boxes are left blank.
Note: Only steroids given IV or PO are included for the purposes of this study. Inhaled steroids **are not** included.

a. Course:
A course is defined as all of the doses given in a period between an initial, usually high dose, and subsequent tapers. It may include a period when drug is given every other day. For the purposes of this study, a course is defined as ended when 72 hours passes without a steroid dose. If 72.5 hours passes and the infant receives another series of doses of the same or a different steroid, this is considered to be a second course.

b-c. Start and Stop Date:
The first and last doses given in a single course. RTI will use these dates to define the duration of exposure in days.

d. Drug:
Record the steroid administered using the following codes:
1= Dexamethasone
2= Betamethasone
3= Hydrocortisone
4= Prednisone
5= Other (Specify the other drug that was given)

e. Total Dose:
Calculate the total dose given in the course expressed as mg/kg. For example, the baby receives a course of dexamethasone beginning at 0.2 mg/kg for 2 days, and subsequent doses given as 0.1 mg/kg given for 2 days, 0.05 mg/kg for 2 days, 0.05 every other day for 2 doses, and then discontinue. The total dose administered to this patient is 0.2+0.2+0.1+0.1+0.05+0.05+0.05+0.05. The total dose administered is 0.8 mg/kg.

If the dose is not expressed in mg/kg in the medical record, the researcher calculates the mg/kg dose using: 1) the weight used in calculating the dose if documented, 2) the weight on the day the order was written to calculate the mg/kg.

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Chapter 15

ROP Outcomes and Tracking Summary

15.1 Introduction

The purpose of this form is to track and document the acute ROP outcome of each eye. Tracking the course of ROP should begin with the first examination and will generally be much easier if the coordinator attends the examinations and asks the ophthalmologist in person about the categories to be recorded.

Data may be entered in the database from the form after each examination, or may be entered when the infant reaches "acute/final" status. However, monitoring of the examinations and progress will be much more complete and helpful if these are entered after each examination.

15.1.1 Instructions for completing the ROP Outcomes and tracking Summary (SUPP10)

Complete this form for all enrollees in SUPPORT who survive to have their first eye examination. This normally is scheduled at 31 weeks postmenstrual age (but not earlier than 4 weeks after birth).

Record the data for each eye examination until each eye has reached "acute/final" status (see definition below in 15.2). This will sometimes include examinations following discharge home or transfer to another hospital.

1. Date of Exam

If a confirming examination is conducted, each should be separately recorded.

2. Location of Exam

Code 1= inpatient for the primary hospital where the infant has been cared for, including other Units in that same hospital (step down units, pediatric intensive care, surgical care units, etc.)

Code 2=Outpatient for examinations in the outpatient ophthalmology department, private ophthalmologist's office or other outpatient visits. Include infants at a chronic care facility transported to the physician's office for an examination.

Code 3= Transfer Hospital when infants have been back transferred to a referring hospital or regional hospital.

Note: Outpatient and back transfer hospitals can be a common source of infants missing examinations and "slipping through the cracks". Be particularly attentive to ensuring timely repeat examinations in these cases and ensure that the family is aware of the importance and critical timing of the examinations.

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3. **Lowest zone:** Record the lowest zone that contains vessels that end before crossing out of that zone. This may be zone I (the most immature), zone II (intermediate) or zone III (most mature). The ophthalmologist normally records this on the eye examination form. The most common for SUPPORT infants will be zone II at the early examinations. There may be vessels recorded in:
   - zone I and II (you record zone I)
   - zone I only (you record zone I)
   - zone II only (you record zone II)
   - zone III only (you record zone III)

   Note that by convention, disease is never to be recorded in zones II and III in the same eye. If the two nasal clock-hours are not fully vascularized, by convention, no vessels in that eye are to be recorded in zone III. If they are fully vascularized, the all the rest of that eye's vessels are in zone III.

4. **Highest stage in lowest zone** (not to be used if eye has had surgery)
   Look first at the lowest zone that has vessels ending in it (see previous answer). Then look to see if there is ROP in any of the clock hours of that zone. Choose the highest stage of ROP in that zone to record.

   Examples:
   If the eye has vessels ending in just zone I, but no ROP, the highest stage is zero.

   If the eye has vessels ending in zone I and zone II and the ROP in zone I is stage 2 while the ROP in zone II is stage 3, the highest stage in the lowest zone (I) is stage 2.

   If the eye has vessels ending in zone I, but there is no ROP in zone I, but there is stage 2 and stage 3 ROP in zone II, the answer would be 0=no ROP in the lowest zone.

5. **Highest stage in any zone** (not to be used if eye has had surgery)
   Look at the stage of ROP around the 12 clock-hours of the recorded examination. Choose the highest stage to record. In rank order going from lowest to highest the order is 0, 1, 2, 3, 4a, 4b, 5. The other categories are for less common cases.
   - Code 4 = stage 4a or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

6. **"Plus disease"**
   This is recorded by the ophthalmologist as present or not. Sometimes they provide comments like 'borderline plus' or 'possible early plus disease' or 'mild dilation, but not plus disease'. In these cases, do not record 'plus disease' as present. If the ophthalmologist records plus disease by quadrants, two or more quadrants are required to meet criteria for plus disease (i.e. only one quadrant of dilated/tortuous vessels is not sufficient.).

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7. Threshold (New Type 1 threshold per ETROP)

The ophthalmologist who diagnoses threshold ROP needing surgery will normally state this prominently on the examination form. The criteria for the new threshold are any of the following four findings:

If in zone I: stage 3 ROP, even without plus disease
plus disease with any stage ROP

If in zone II: plus disease with stage 2 ROP
plus disease with stage 3 ROP

There may be times when disease is worse than this, but it should still be recorded as threshold.

There will be some times when the judgment of the retinal surgeon and neonatologist will be not to administer treatment (laser or cryo), even when there is new threshold. Normally infants are then followed extremely closely (every few days repeat examinations).

8. Surgery

For each examination date, record if surgery is performed on that day. (mostly will be no). If surgery was previously performed, but not on the day of that examination, record 0

9. Post-surgical Retinal Detachment after surgery

This at first looks like a repeat of the question asking for stage of ROP, but it is not since it is intended to be used only after surgery has occurred.

10. Final Acute Status Lost to Follow-up at 55 weeks PMA

Complete this question **only** for the final eye exam entered.

Record 'N' if the last examination meets criteria for final acute status reached (see section 15.2 below).

Record 'Y' if the final 'acute' ROP status is permanently missing because the infant is lost-to-follow up. For example, the last exam is not yet mature, or not yet in zone III for the second time in a row, or the baby still has ROP, but had not reached criteria for surgery. All attempts must have been made to capture this data from the follow up exams, and it is coded 'Y' as missing only when there was no final exam done (parents did not bring infant in).

By the time an infant has reached 55 weeks PMA, the eye disease will have reached final status, whether we know about it from an examination or not. That is why we make this determination at this time. If it is later learned that examinations actually were done, the results can be entered on the form with a late correction/edit.

Therefore, if you know the infant is less than 55 weeks PMA and has not had an exam that meets the final/acute criteria, you are still trying to get the family to bring the baby in for exams because it is clinically important and also will give you a primary

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study outcome. If it is now past 55 weeks, you may give up trying to get them to come in because it's too late to identify disease that could be treated, and the time for the clinical outcome for the study is also past. Late outcomes will be collected at the 18-22 month follow up examination.

Potential merit of later exams: Most likely, they will reassure the infant that the eyes have healed. They may detect an important need for glasses at 6-9 months after birth. If the outcome is retinal detachments, the parents will learn the baby is not going to see and needs to be referred for early intervention. In either event, late exams that show retinal detachments will confirm that once upon a time, the baby did have bad ROP. Late exams that show good outcomes will NOT tell us if they once had ROP that has now regressed (healed).

Note: even in these circumstances where we have given up, the infant will still be tracked down for the 18-22 month follow up visit. At that time they are asked if any eye surgery was done after discharge / status. If yes, what surgery. If it was for ROP, then that will become a final status revision. Also, even if no surgery was done, but the child has experienced vision loss *from ROP*, this would also be a final outcome.

Note that some infants have vision loss that is not from ROP. This is usually "cortical vision loss" and is from brain injury.

11. Final ROP Status determined at 18 Moth Follow Up
Complete this question **only** for the final eye exam entered.

Answer this question as 'N' if the final acute status was already determined before 55 weeks PMA. That is, "no, we did not determine the final outcome based on the 18-22 month exam."

Also, answer this question as 'N' if the final status was not determined by 55 weeks PMA, AND it was not determined at the 18-22 month visit either. This would happen if there were no 18-22 month examination. It would also happen if there were an 18-22 month examination, but the parents report no eye surgery and no other eye exams so we don't know what happened to the ROP.

You can record 'Y' for the final ROP status obtained during the 18-22 month follow up visit only if the parents are now reporting to you eye surgery for ROP that you had not learned about before, or they are telling you about eye exams that you have not learned about before (or else you would have recorded it before). If this is the case, reports from the exam(s) and/or surgery should be obtained to determine what has happened. These data will likely require ophthalmology input to determine if the primary ROP outcome was reached. Examples: A. ROP can be assumed (imputed) to have reached surgical criteria if the infant's subsequent surgery is vitrectomy for retinal detachment, or is an exam under anesthesia with a diagnosis of ROP stage 4A, 4B or stage 5 ROP, or retinal fold crossing the macula. B. ROP may not have met laser/CRYO criteria if the surgery was for strabismus (crossed eye), plugged tear duct, or only examination under anesthesia, for example to rule out glaucoma.

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15.2 Acute/final Status

An eye is 'acute/final" when it reaches one of the following points in time:
These can be a good outcome (favorable) as the ROP heals (regresses), or it can be the primary outcome variable event (unfavorable).

Favorable

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5 retinal detachment stage 4b

Other

- Infant dies.

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Chapter 16

Respiratory Support after 14 Days

16.1 Introduction

The purpose of this form is to document any respiratory support the infant receives after day 14.

16.1.1 Instructions for completing the Respiratory Support Form after 14 Days (SUPP11)

This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 8= Infant temporarily out of unit 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

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infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

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Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b) [redacted]

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

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contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

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Select the button twice.
Select the icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

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17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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APPENDIX A

STUDY FORMS

SUPP01	**Screening Log**
SUPP02	**Eligibility Form**
SUPP03	**Delivery Form**
SUPP04	**NICU Admission Form**
Supp04a	**NICU Admission Form (Surfactant Doses)**
SUPP05	**Safety Monitoring Form**
SUPP06	**Protocol Deviation Form**
SUPP07	**Reintubation Form**
SUPP08	**Adverse Event Form**
SUPP08A	**MedWatch Form**
SUPP09	**Outcome Status Form**
SUPP10	**ROP Outcomes and Tracking Summary**
SUPP11	**Respiratory Support After 14 Days**

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APPENDIX B

SAMPLE CONSENT FORM

University of California, San Diego
Consent to Act as a Research Subject

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age).

The purposes of this trial are the following:
1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two year period.

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

If you agree to allow your child to be in this study, the following will happen to your child:
Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine).

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In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter (a monitor that displays how much oxygen is in the blood). The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.

Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e. g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). Other care will be conducted as normal during his/her participation in the study. Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive, at no charge to you, a complete exam of their muscles, nerves, and mental and coordinated movement skills.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

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As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so.

You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights

You agree to have your child participate.

_____

Parent's or legal guardian's signature DATE

_____

Relationship of legal guardian to subject DATE

_____

Signature of person explaining and getting consent DATE

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APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

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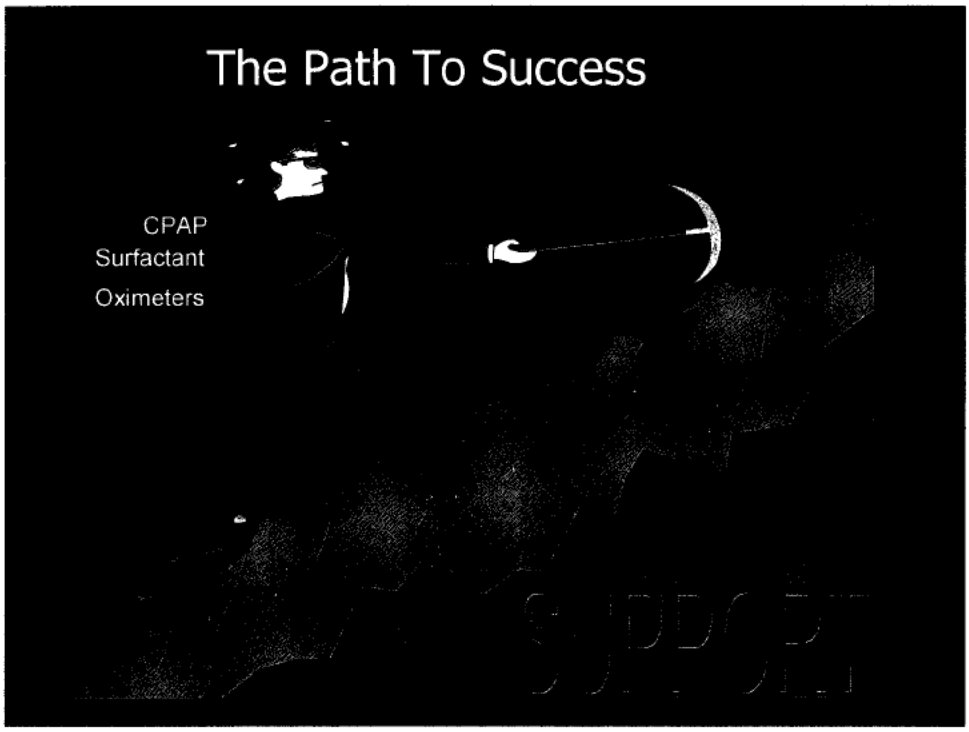
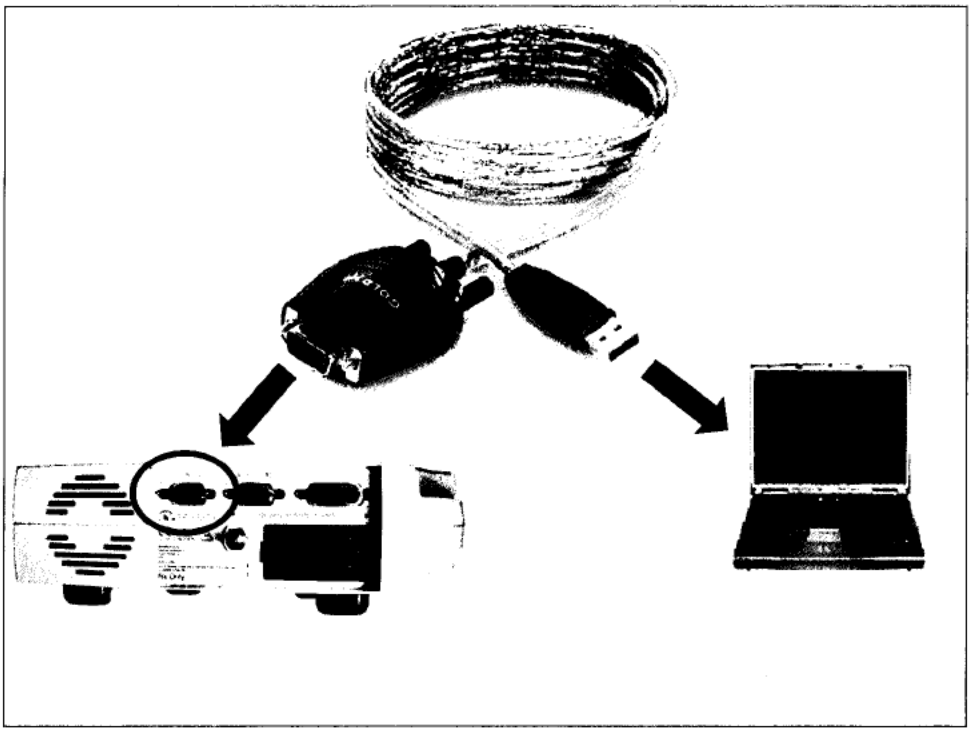
APPENDIX D

SUPPORT DOWN LOAD





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Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

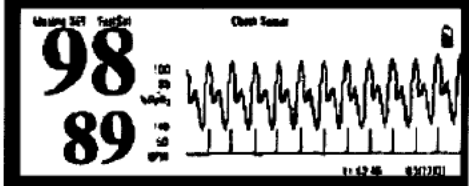
Use arrow key to select "Binary".

Select button.

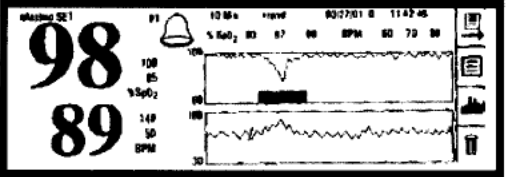
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

Make sure the Radical is in run mode and not in mode.



YES



No

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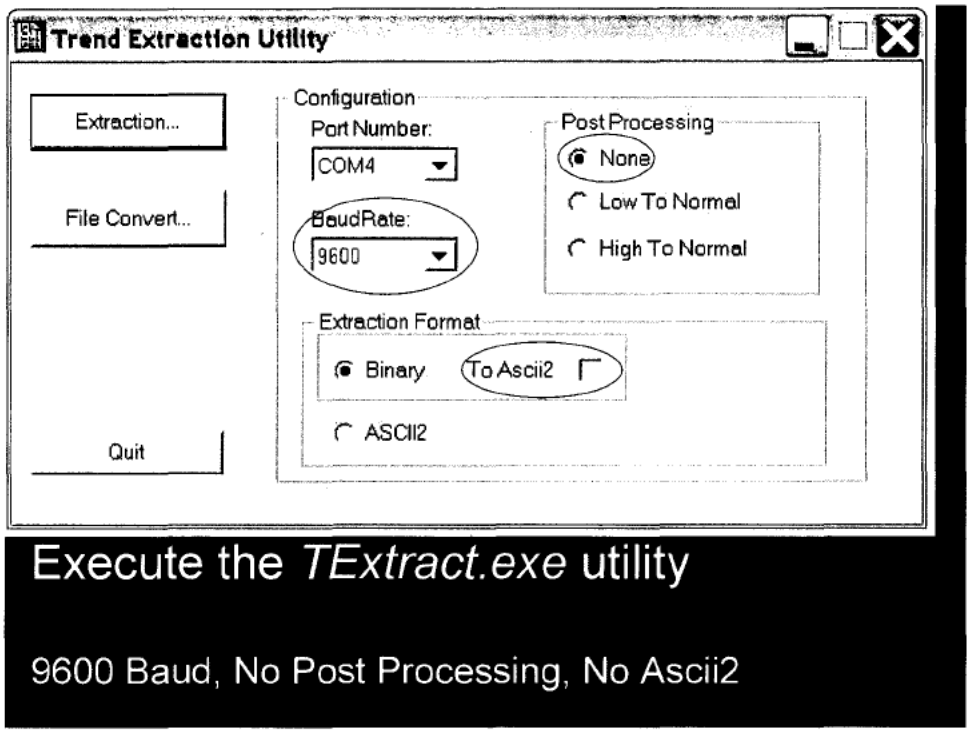
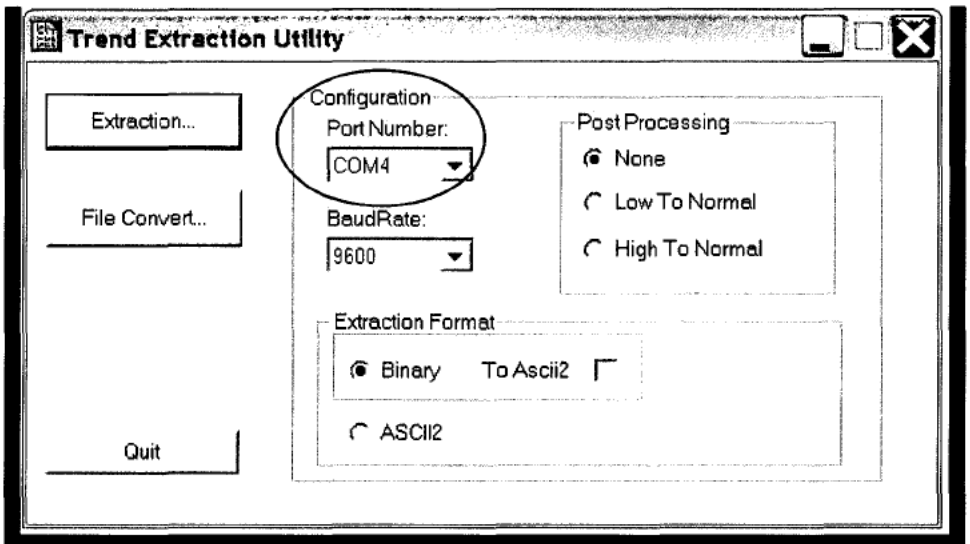


Execute the *TExtract.exe* utility

9600 Baud, No Post Processing, No Ascii2



In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

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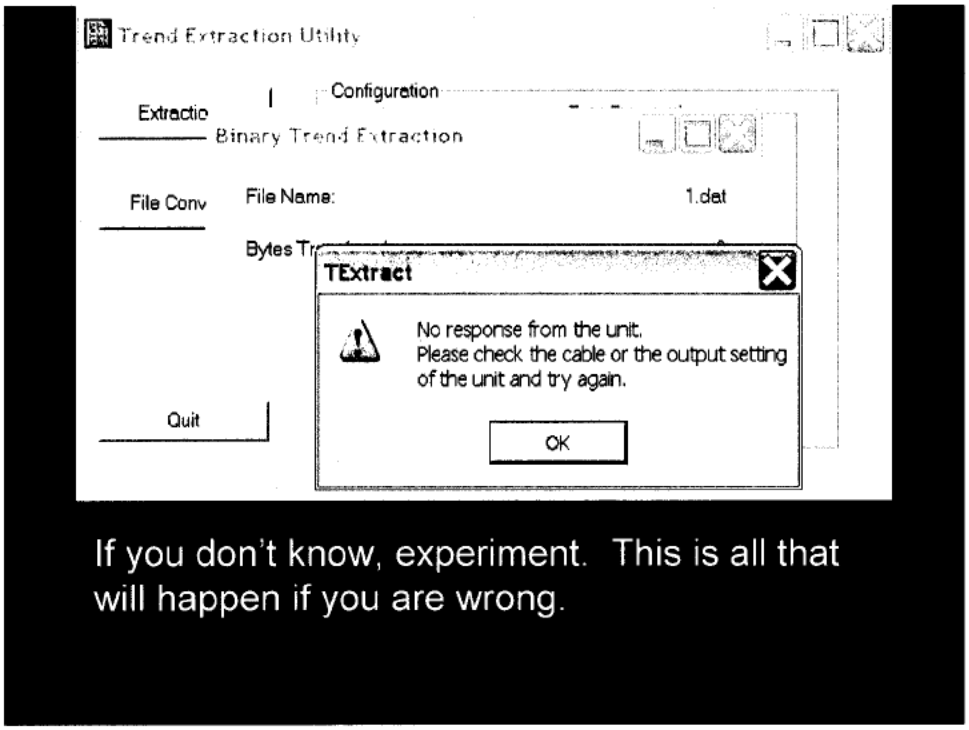
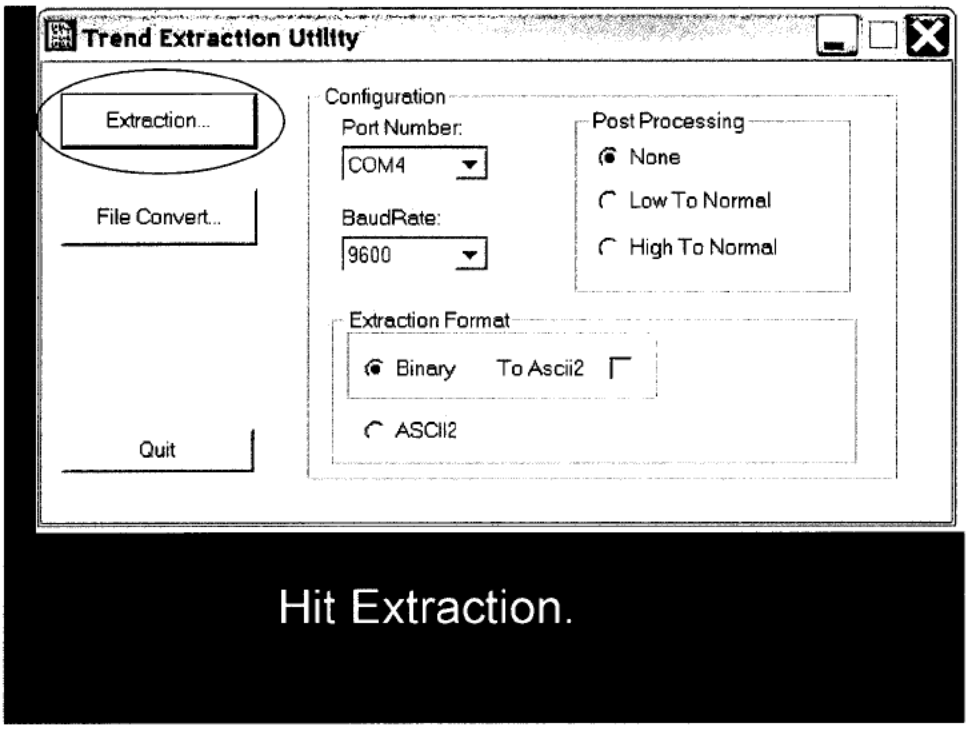


If you don't know, experiment. This is all that will happen if you are wrong.



Hit Extraction.

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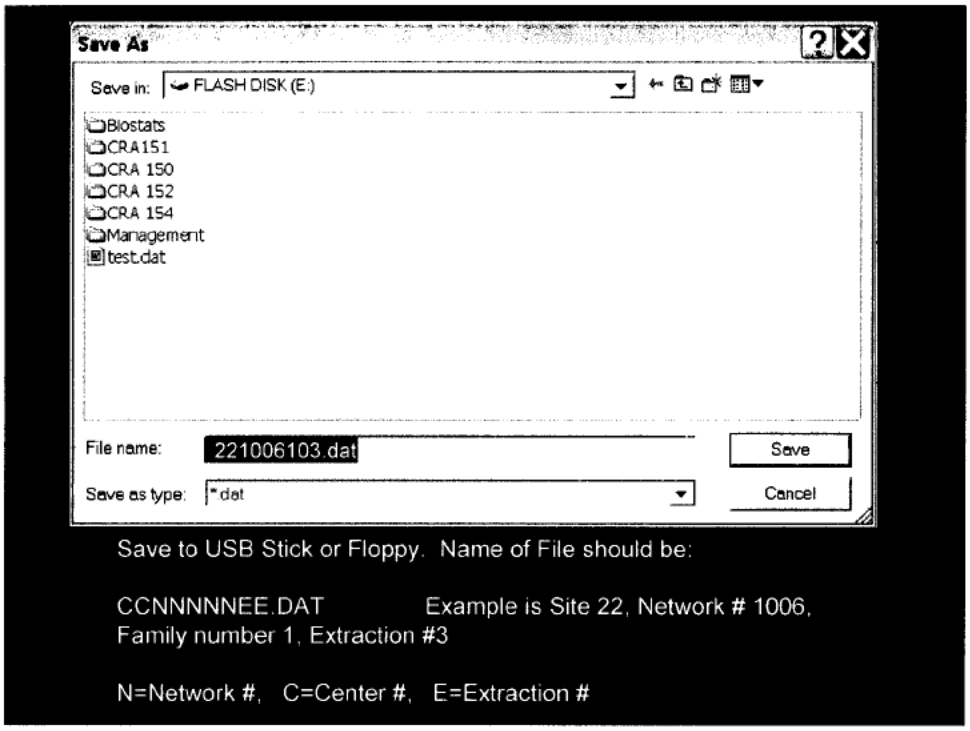

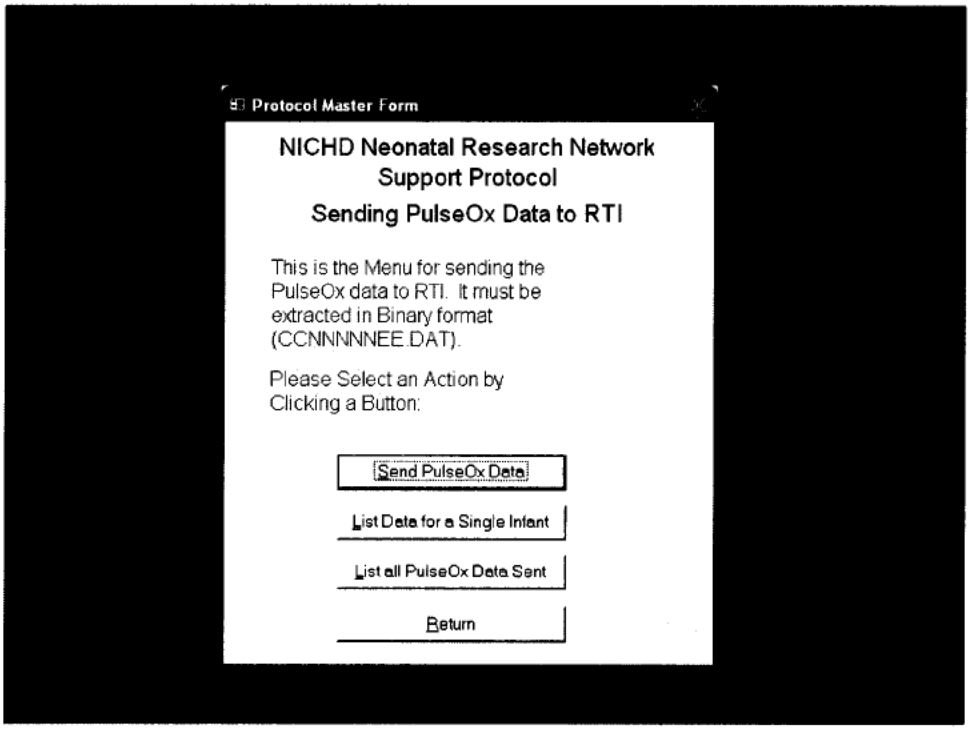

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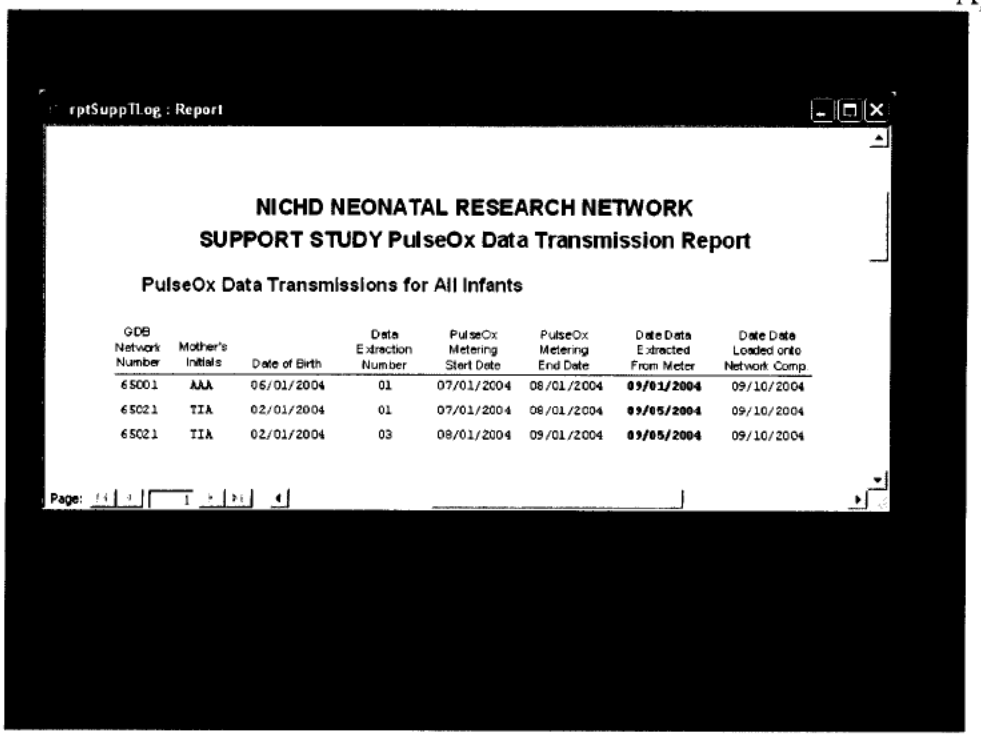
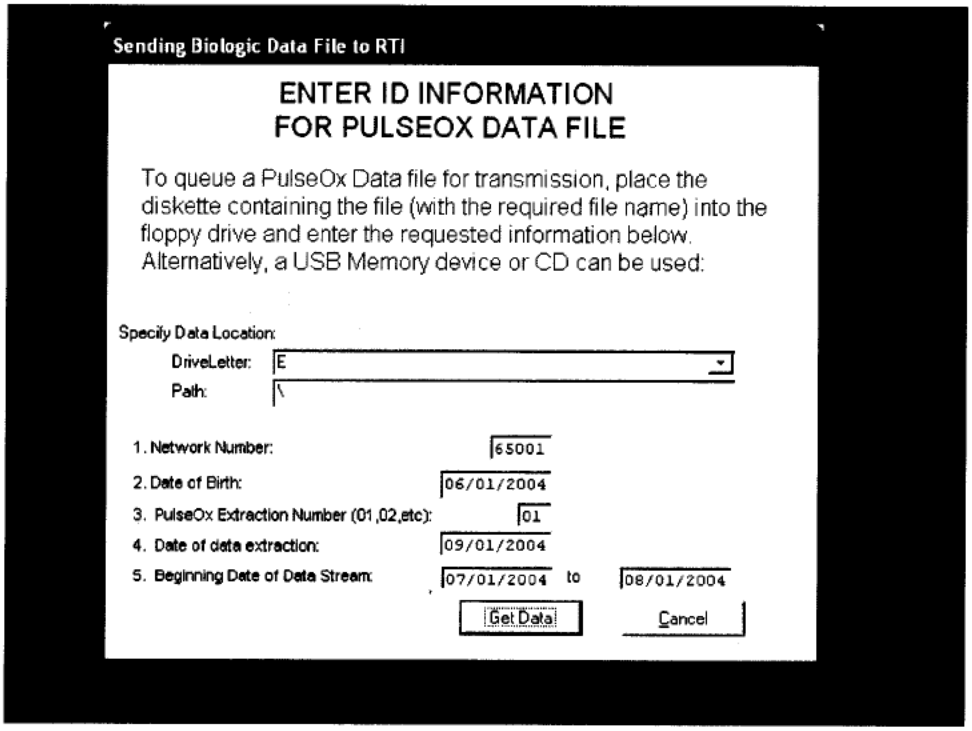

rptSuppTLog : Report

NICHD NEONATAL RESEARCH NETWORK
SUPPORT STUDY PulseOx Data Transmission Report

PulseOx Data Transmissions for All Infants

GDB Network Number	Mother's Initials	Date of Birth	Data Extraction Number	PulseOx Metering Start Date	PulseOx Metering End Date	Date Data Extracted From Meter	Date Data Loaded onto Network Comp
65001	AAA	06/01/2004	01	07/01/2004	08/01/2004	**09/01/2004**	09/10/2004
65021	TIA	02/01/2004	01	07/01/2004	08/01/2004	**09/05/2004**	09/10/2004
65021	TIA	02/01/2004	03	08/01/2004	09/01/2004	**09/05/2004**	09/10/2004

Page: 1


Sending Biologic Data File to RTI

ENTER ID INFORMATION FOR PULSEOX DATA FILE

To queue a PulseOx Data file for transmission, place the diskette containing the file (with the required file name) into the floppy drive and enter the requested information below. Alternatively, a USB Memory device or CD can be used:

Specify Data Location:
DriveLetter: E
Path: \

1. Network Number: 65001
2. Date of Birth: 06/01/2004
3. PulseOx Extraction Number (01,02,etc): 01
4. Date of data extraction: 09/01/2004
5. Beginning Date of Data Stream: 07/01/2004 to 08/01/2004

Get Data | Cancel

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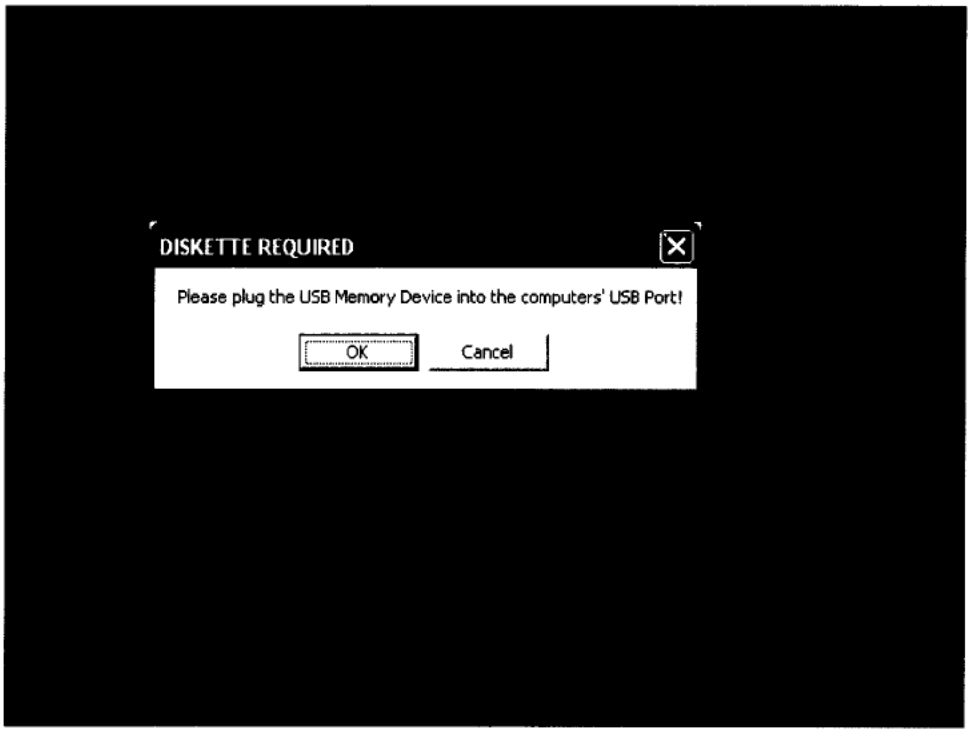
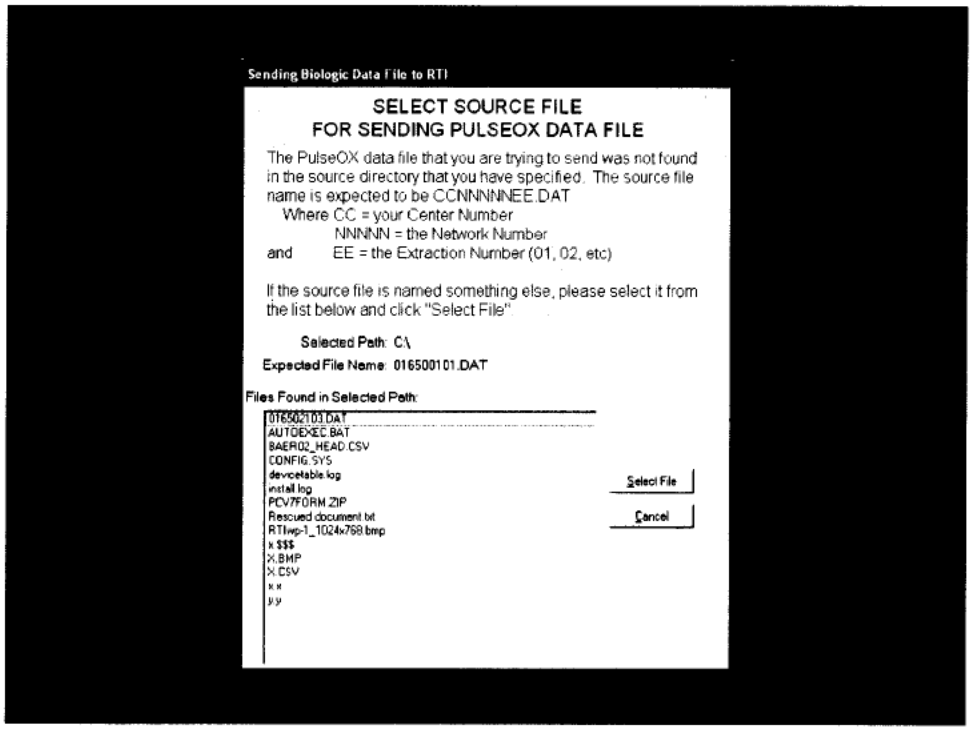
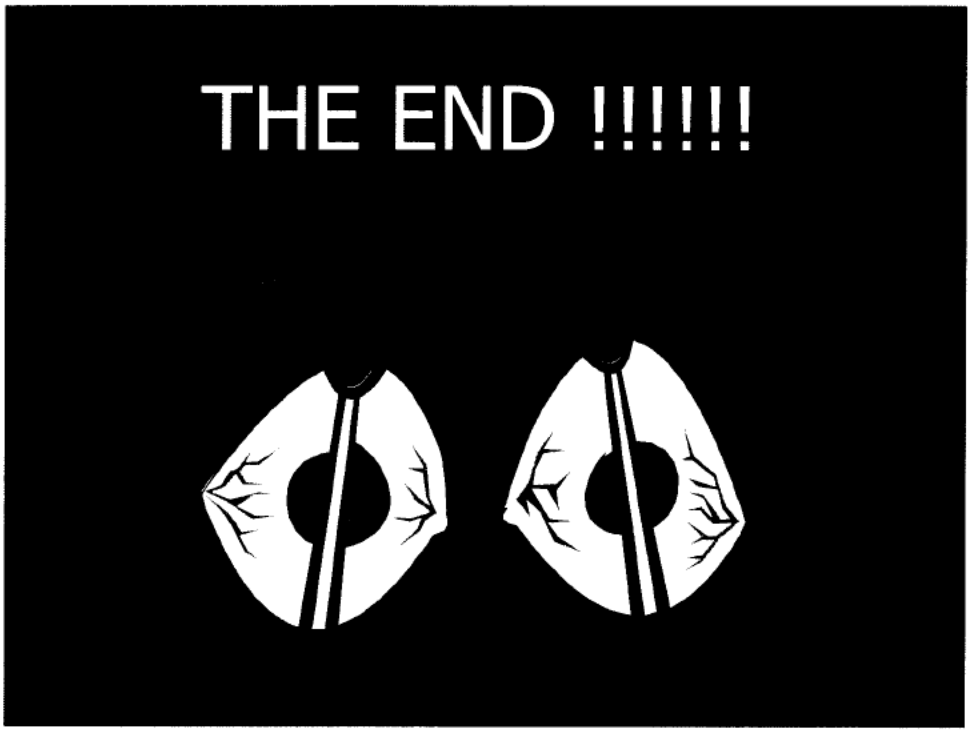




This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.



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APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

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SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

 # xxxx

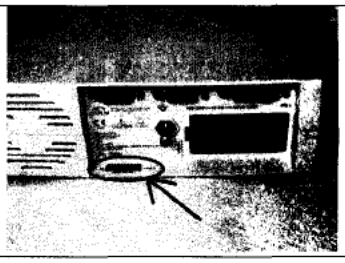
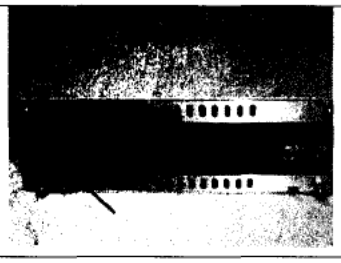
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

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APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No infant will be subject at any time to repeated swings in the amount of O2 being delivered in response to the saturation readings outside the acceptable range.

STATEMENTS OF PRACTICE:

a. Oxygen is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - Weaning should be done as fast as necessary to avoid extended periods of hyperoxia. (But not faster than 2-5% at a time)

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- Avoid weaning in increments >5% at a time; this could result in hypoxia, which would then lead to increasing the FiO2 again.

e. Increasing the FiO2 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- MD/NNP must be notified for any sustained need for an increase in FiO2 greater than 10% from the previously stable FiO2.

f. During and after procedures:
- FiO2 should not be routinely increased prior to a procedure. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. Respond appropriately to the needs of the infant based on the saturations as well as the length and type of procedure.
- Monitor the infant after suctioning the ETT until the baby returns to their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, tactile stimulation, or in severe cases manual ventilation.
- If the baby does not return to the previously stable baseline (same FiO2) within 10 minutes, the MD/NNP should be notified.

SUMMARY:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

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2. Allow baby to fluctuate within the desired saturation parameters, making small movements up and down on FiO2 as needed.
3. Based on assessment, wean actively by 2-5% for saturations on the high side of parameters.
4. Never increase the FiO2 without first assessing the baby.
5. If the need for increased FiO2 is sustained, the MD/NNP should be notified.
6. Document saturation levels and oxygen requirements clearly (as per unit policy).
7. When altering the oxygen being delivered stay with the infant until the saturations have stabilized within an acceptable range.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

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APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

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From: Rich, Wade
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP queries Center 22 09OCT09
Date: Monday, October 12, 2009 12:19:26 PM

(b) (6) is Mature, so Nf05 and NF09 are not relevant at this time. NF05 and 09 are f/u forms, which were completed at his visit on September 29th. They were entered this AM and will be transmitted Tues.

(b) (6) was marked as 'missing' per Rose's request on September 25th because he had not been seen in F/U yet. He has had 19 visits, but has not had 2 zone three exams. His f/u is not until
September of 2010, and his next eye visit is not due until November.

Wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 2:11 PM
To: Finer, Neil; Rich, Wade
Subject: SUPPORT ROP queries Center 22 09OCT09

We have queries and a few missing items for SUPPORT.

thanks for all your help

Rose

22	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		FU window has closed but NF05 and NF09a have not been completed.

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From: Bara, Rebecca
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; Sood, Beena; Pappas, Athina
Cc: "Gantz, Marie"
Subject: RE: SUPPORT ROP queries Center 5 09OCT09
Date: Monday, October 12, 2009 12:15:41 PM

Thanks for the reminder, we're still working on these.

Becky

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 4:55 PM
To: Shankaran, Seetha; Sood, Beena; Bara, Rebecca; Pappas, Athina
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 5 09OCT09

CENTER NETWORK ROP_message
5 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
5 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
5 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
CENTER NETWORK FU_message
5 (b) (6) FU window has closed but NF05 and NF09a have not been completed.

We are finalizing the SUPPORT data. ROP queries are in the email and the attachment. We intend to lock the data base on 10/20 following DMS transmission.

Thanks for all the help

Rose

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From: Wally Carlo, M.D.
To: Laptook, Abbot
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Calls- SUPPORT Call
Date: Sunday, October 11, 2009 6:29:27 PM

Abbot:

Thanks for your thoughtful comments. I will work on them. I am trying to keep the paper under the 2700 word limit but will try to see what can be added of your suggestions.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Sunday, October 11, 2009 5:02 PM
To: Wally Carlo, M.D.
Cc: nfiner@ucsd.edu; HigginsR@mail.nih.gov
Subject: RE: NRN Calls- SUPPORT Call

Wally
Nice start to an obviously very important paper. Here are some comments.

1) Methods/enrollmen/treatment: we should point out that the target ranges applied when infants were in O2 and when in room air the upper alarm limit could be raised.
2) Methods, offset of 3%: It would help many readers to know that the offset is the value when the device is reading 90% and that when the device is reading higher values approaching 95% the offset decreases in magnitude. The same concept for when the lower limit is appraoched.
3) Methods: Don't we need to list the downloads of data and processing by RTI with feedback to the centers for time spent with different saturation ranges? This is a very important difference from the literature which everyone sites on the effects of lower oxygen saturation policies without knowledge of where the saturations are.
4) Results/major outcome section: The sentence "The PIs and the NICH D and data center performed a detailed analysis..." is a little unclear regarding the timing of this. If this is left as is, it needs to be clear that not all ROP results are not final since 55 weeks has already occurred.
5) Other major outcomes were comparable? Is BPD (oxygen at 36 wks) different?
6) Median oxygen saturations of each group: can you provide IQR?
7) Results of oxygen saturations: I think you need to present more data to characterize the oxygen saturations while in oxgyen. A table would be helpful for the percent of time with oxgyen saturations >98, 96-98, 93-95, 88-92, 85-87, 80-84 and <80% for each group.
8) Are you going to present age of deaths and assigned causes of death?
9) Table 1: consider including some additional maternal data (chorio/maternal antibiotics, mode of delivery etc)
10) Figure 1: I don't see a number for all the consented mothers who passed thru the gestational age window of the study.

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11) Discussion: As I am sure you are aware there are limited data on the ability to maintain oxygen saturations within desired ranges. I think there needs to be some mention of this with regards to figure 2 (see Pediatrics 2006;118;1574-1582) and that even very small changes in goal ranges for oxgyen saturation can lead to an increase in oxygen saturation at the low end (J Perinataology 2006;26;337-341)

Hope this helps, tx, AL

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, October 07, 2009 11:34 AM
To: Huitema, Carolyn Petrie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Laptook, Abbot; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject: RE: NRN Calls- SUPPORT Call

I would like to get comments on the O2 sat paper from the committee members. I have heard from Rose, Neil, Marie and Abhik as we had worked on the previous draft. I would appreciate any comments as soon as possible so I can have with everyone's input by the SC meeting.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Wednesday, October 07, 2009 8:26 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Wally Carlo, M.D.; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject: RE: NRN Calls- SUPPORT Call

Reminder for today's call:

Materials for this call are attached to the email.

The SUPPORT call has been scheduled for

Wednesday, October 7th
SUPPORT 10:30-11:30am ET

For all calls please dial

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Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From:	Finer, Neil
To:	Wally Carlo, M.D.; Huitema, Carolyn Petrie; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc:	Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject:	RE: NRN Calls- SUPPORT Call
Date:	Sunday, October 11, 2009 6:25:38 PM
Attachments:	SUPPORT CPAP vs Surf Oct 06 09 .docx Tables Aug 29.docx

Hello Everyone
I thought that this went to all the Subcommittee – Please review the SUPPORT Manuscript for CPAP vs Surf. Your input is essential. Marie will insert the final numbers etc once we have the results of all the queries.
I look forward to your comments and critiques
Many thanks
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, October 07, 2009 8:34 AM
To: Huitema, Carolyn Petrie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject: RE: NRN Calls- SUPPORT Call

I would like to get comments on the O2 sat paper from the committee members. I have heard from Rose, Neil, Marie and Abhik as we had worked on the previous draft. I would appreciate any comments as soon as possible so I can have with everyone's input by the SC meeting.

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Sent: Wednesday, October 07, 2009 8:26 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Wally Carlo, M.D.; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject: RE: NRN Calls- SUPPORT Call

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The SUPPORT call has been scheduled for

Wednesday, October 7th
SUPPORT 10:30-11:30am ET

For all calls please dial

Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Address correspondence to

Neil Finer, MD

402 Dickenson St, 8774

San Diego, Ca, 92103-8774

Email – nfiner@ucsd.edu

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Comment [AD1]: Should we rephrase this? Sounds like the infants themselves gave consent!

Results: The study enrolled 1317 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group (all p<0.001), and 67% of the CPAP infants received surfactant at any time during their hospitalization,. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, p=0.03). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants requiring intubation during their nursery course, (p<0.001). There were no differences between the groups for air leaks including pneumothoraces.

Comment [AD2]: I would provide the relative risk and 95% CI instead of, or in addition to the p value. Same goes for other CPAP vs surfactant outcome comparisons, both here and in the main text.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months.

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Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation

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or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses46, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Comment [AD3]: We should be consistent in either picking death or BPD, or survival without BPD.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

Comment [AD4]: Since we are not reporting NDI here, and did not adjust our sample size for multiple outcomes, do we need to say this?

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

Comment [AD5]: Let us make the statistical sections of both primary papers as similar as possible.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

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Results:

There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, $p=0.27$. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (40% vs 41%, $p=0.96$), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, $p=0.32$).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.01$). There were no differences between the groups in air leaks in the first 14 days, air leaks during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, $p<.001$).

Strata Results: 24 – 25 weeks Gestation

Comment [AD6]: Do we need to preface some justification for looking within strata?

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There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p<0.01, lesser days of mechanical ventilation, 10.7 vs 14.2, p<0.01, and less postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[14,14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.**8 We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. We also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe

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that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0552

Table 2. Delivery Room interventions

Variable	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Apgar at 1 minute <3	23% (154/662)	26% (167/652)	0.3214
Apgar at 5 minutes <3	4% (26/664)	5% (32/652)	0.3806
PPV in the DR (per SUPP03)	66% (435/662)	93% (605/651)	<0.0001*
CPAP in the DR (per SUPP03)	81% (539/663)	22% (146/652)	<0.0001*
Surfactant in DR (per SUPP03)	14% (93/659)	51% (334/651)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)	67% (443/660)	99% (645/652)	<0.0001*
Chest compressions in DR (per SUPP03)	5% (36/660)	6% (40/652)	0.5978
Epinephrine in DR (per SUPP03)	2% (13/660)	4% (27/652)	0.0222*
Death in the DR (per SUPP03/SUPP04)	0% (1/663)	1% (6/652)	0.0552

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9797
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	99.9 ± 42.6	100.5 ± 39.4	0.8210
Days on supplemental oxygen (survivors only)	53.9 ± 37.2	57.4 ± 37.0	0.1138
Days on mechanical vent (HFV & CV) (survivors only)	19.0 ± 22.8	22.0 ± 24.8	0.0392*
Days on CPAP (survivors only)	16.1 ± 13.2	16.0 ± 14.6	0.9229
Discharge on oxygen	22% (120/547)	24% (121/514)	0.5334
Alive and off MV (HFV/CV) at 7 days	55% (362/654)	49% (316/650)	0.0149*
Any air leak in first 14 days	7% (44/664)	8% (49/652)	0.5293
Medical or surgical NEC	13% (83/655)	10% (62/634)	0.1004
PDA requiring surgery	11% (73/654)	11% (68/634)	0.8019
IVH grade 3-4	15% (95/644)	13% (80/627)	0.3027
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0004*

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/279)	0.5127
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.0 ± 47.4	118.6 ± 39.6	0.7514
Days on supplemental oxygen (survivors only)	75.7 ± 34.1	76.8 ± 33.1	0.7500
Days on mechanical vent (HFV & CV) (survivors only)	32.1 ± 26.6	35.8 ± 27.8	0.1672
Days on CPAP (survivors only)	18.6 ± 13.9	17.7 ± 15.5	0.5496
Discharge on oxygen	32% (68/212)	31% (57/185)	0.7867
Alive and off MV (HFV/CV) at 7 days	34% (97/282)	26% (73/279)	0.0339*
Any air leak in first 14 days	8% (22/285)	10% (28/280)	0.3399
Medical or surgical NEC	15% (42/279)	13% (34/267)	0.4338
PDA requiring surgery	16% (46/279)	18% (47/267)	0.7289
IVH grade 3-4	19% (53/273)	19% (50/265)	0.8722
Postnatal steroids for BPD	13% (36/276)	21% (54/263)	0.0198*

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: extended SUPPORT MRI follow-up
Date: Sunday, October 11, 2009 5:55:03 PM
Attachments: FINAL_SchoolAgeFollowUpSUPPORTNeuroimagingPDF.pdf

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Hi Rose

Here is the protocol with Krisa's name back on the front page. I have no idea when or where it dropped off.

Thanks -

Susan
--
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Extended Follow-up at School Age (6½ to 7½ years) for the SUPPORT Neuroimaging and Neurodevelopmental Outcomes Cohort

Subcommittee:

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I) INTRODUCTION:

The **Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)** is a prospective, randomized, factorial 2x2 design multi-center trial conducted by the NICHD Neonatal Research Network (enrollment completed February 2009). The trial will evaluate if CPAP and a permissive ventilation strategy and lower SpO_2 targets (85-89% vs. 91-95%) will result in increased survival without bronchopulmonary dysplasia (BPD) and increased survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. **The SUPPORT Neuroimaging and Neurodevelopmental Outcomes Study** is a prospective secondary study to SUPPORT of cranial ultrasound (CUS) at 4-14 days ("early CUS") and 35-42 weeks postmenstrual age (PMA) ("late CUS"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT. The study was launched in May 2005, and 16 NICHD NRN sites participated. This study will allow us to assess the comparative and combined capabilities of early and late CUS and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age. The SUPPORT Neuroimaging and Neurodevelopmental Outcome cohort will be the largest such cohort assembled to date.

Children born extremely prematurely continue to have significant neurodevelopmental challenges in later childhood, yet many subtle but significant cognitive and performance problems cannot be delineated until school age. Early and accurate prediction of neurodevelopmental outcome would be invaluable, but CUS and other early variables do not reliably predict outcomes. White matter (WM) injury has been strongly implicated in neuromotor and cognitive impairment, and a link between WM injury and gray matter developmental disruption appears to exist. MRI is better than CUS in identifying subtle and diffuse WM injury, as well as cerebellar and gray matter abnormalities. Previous studies of preterm infants have shown WM injury by MRI to be significantly associated with CP and adverse *neurosensory* outcome, independent of CUS abnormalities. An independent association with *cognitive* impairment in early childhood has not yet been demonstrated. However, subtle neonatal MRI abnormalities may predict cognitive problems in early school age that cannot yet be delineated at 18-24 months. In addition, higher rates of behavioral and executive function impairments in childhood have been reported among very preterm infants, and previous studies have suggested that WM injury seen on neonatal MRI may predict these impairments. **We therefore propose to follow the SUPPORT Neuroimaging cohort at 6½ - 7½ years to test the primary hypothesis that neonatal brain MRI is superior to neonatal CUS in predicting death after discharge or cognitive impairment (Wechsler Intelligence Scale for Children-IV (WISC-IV) IQ<70) at school age.** We will also test whether neonatal brain MRI is superior to CUS in predicting neuromotor impairment, disability, and less severe cognitive impairment. We will also assess whether injury severity on neonatal MRI is associated with longitudinal cognitive and disability level changes, examine cognitive impairment and disability between ventilatory and oxygenation saturation SUPPORT intervention groups, and determine whether neonatal MRI is superior to CUS in predicting adverse executive and behavioral outcomes.

The SUPPORT Neuroimaging cohort is valuable and unique among other preterm cohorts worldwide. By pursuing 6½ - 7½ year follow-up, the NICHD NRN is in an outstanding position to substantially contribute to our understanding of later extremely preterm outcomes and their prediction.

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II) HYPOTHESES:

Among children enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary with complete neuroimaging and surviving to hospital discharge:

PRIMARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment (WISC-IV IQ<70) at 6½ - 7½ years.

SECONDARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment (WISC-IV IQ<70) at 6½ - 7½ years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or disability, or disability among survivors, at 6½ - 7½ years.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the risks of cognitive impairment, disability, or neuromotor impairment including CP between ventilatory or oxygenation saturation SUPPORT intervention groups in this sub-cohort.
- Neonatal brain MRI will be superior to neonatal CUS in predicting mild cognitive impairment (WISC-IV IQ 1-2 SD below population mean) at 6½ - 7½ years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting CP and neuromotor/movement impairment at 6½ - 7½ years.
- Moderate to severe white matter injury on neonatal neuroimaging will be associated with behavior and executive function impairments at 6½ - 7½ years.
    - Neonatal brain MRI will be superior to neonatal CUS in predicting behavioral and executive function impairments at 6½ - 7½ years.
- Severe developmental impairment and severe cerebral palsy at 18-22 months will be highly predictive of severe disability at school age, but mild or moderate impairment at 18-22 months will be poorly predictive of later outcome group.
- Injury severity and pattern on neonatal MRI will be associated with longitudinal cognitive and disability level changes (18-22 months corrected age → 6½ - 7½ years).
- Brain injury pattern and topography on neonatal MRI will be associated with anatomic and functional type of CP at school age.
- High rates of health-related quality of life challenges and chronic or disabling conditions will be observed.
    - These findings will be associated with moderate-severe brain injury on neonatal neuroimaging.
- Local readings of neonatal MRI will be less predictive of 6½ - 7½ year outcomes than central reading.

Specific Aims:

- To assess cognitive, neuromotor, functional and behavioral outcomes of the SUPPORT Neuroimaging cohort at 6½ - 7½ years of age
- To examine the independent associations of neonatal neuroimaging findings with neurodevelopmental outcomes
    - Assess the absolute and relative value of early and late neonatal CUS and neonatal MRI, alone and in combination with other risk factors, to predict normal and impaired outcomes

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- To examine longitudinal changes in cognitive and overall impairment level from 18-22 month to 6½ - 7½ year exams, and assess relationship of neonatal neuroimaging abnormalities and other variables.
- To compare 6½ - 7½ year neurodevelopmental outcomes of ventilation and oxygenation SUPPORT randomized groups in this sub-cohort.

II) BACKGROUND AND SIGNIFICANCE:

Long-term neurodevelopmental outcomes of extremely preterm infants:

Despite advances in perinatal and neonatal management and improvement in survival, short-term neurodevelopmental outcomes of extremely preterm and extremely low birth weight (ELBW) infants remain guarded (Vohr, Hintz #1, Hintz #2, Costeloe). This high frequency of disability in very early childhood (18-24 months) makes longer-term neurodevelopmental outcome studies crucial. Evaluation at a later age allows identification and delineation of a broader range of problems, including cognitive delay, more subtle motor, movement, and coordination disabilities, and behavioral and executive function problems to be determined. It also allows for assessment of the strength of perinatal and neonatal variables as potential predictors of long-term outcomes, and for longitudinal analysis to determine the predictive value of early disability.

Later childhood follow-up studies have demonstrated that significant neurodevelopmental and cognitive impairment continue for extremely preterm infants. In the 206 ELBW infants followed at 5 years in the Finnish National Cohort (Mikkola), 20% had major disabilities, and 19% of those <27 weeks were diagnosed with cerebral palsy (CP). The EPICure Study Group (Marlow) reported on 241 <26 week survivors at 6 years; severe overall cognitive delay was present in 21% compared with test norms (41% compared with term controls), and disabling CP was diagnosed in 13%. In a study of 219 ELBW infants at 8 years (Hack #1), Hack, et. al. reported CP in 14%, severe cognitive impairment in 15%, moderate-severe cognitive impairment in 38%, and significant motor skills problems in 27%. Families reported substantial functional limitations, including emotional delay, trouble understanding or communicating, and need for medication or equipment. Needs for special services were significantly greater than for the normal birth weight (NBW) control group. Impairment in academic (32%) and adaptive skills (48%) have also been reported among ELBW children, and are significantly more frequent than in NBW controls (Taylor). In an ELBW or <28 week EGA cohort at 8 years (n=275), Anderson, et. al. reported significant impairment across all tested cognitive and educational abilities compared with NBW controls (Anderson #1). Although improvements in neurosensory impairment rates have reported over time with successive ELBW birth cohorts in VICS since the 1970's, neurologic disabilities continue to be substantially more common among ELBW children at school age than their normal birth weight peers (Doyle #1).

Summary: Children born extremely preterm or ELBW continue to have significant motor and cognitive disabilities in childhood, as well as more subtle functional and adaptive impairments. Delineation of some of these problems may not even be reasonably undertaken until 5-8 years of age. The true impact of these impairments may not be felt until later school age (Saigal).

Neonatal CUS and other variables to predict neurodevelopmental outcomes

CUS and short-term outcomes (18-24 months)

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The association of severe neonatal CUS abnormalities and adverse short-term neurodevelopmental outcome has been reported in numerous studies (Vohr, Hack #2). But the strength of this association appears to be consistent primarily for combined developmental and neuromotor endpoints, or for CP or motor disability alone, but not for pure cognitive delay (deVries, Hack #2, Wood). In addition, severe CUS abnormalities are not uniformly predictive of adverse short-term outcome and normal CUS do not predict normal outcome in this high-risk population (deVries, Hack#2, Laptook, Ancel, Pinto-Martin). In fact, in a predictive modeling analysis, Ambalavanan found that severe grade of IVH explained only 8% of the variance in low MDI and 5% of the variance for major handicap at 18-22 months (Ambalavanan).

CUS and long-term outcome (5-8 years)

Reported associations of neonatal CUS findings and long-term outcomes are inconsistent. Sherlock, et. al. (Sherlock) reported that neurodevelopmental impairment at 8 years varied little with increasing severity of IVH; a trend for worse cognitive and neurosensory outcome with higher grade IVH in that study was explained solely by the outcomes of the small number of patients with parenchymal hemorrhage. The Neonatal Brain Hemorrhage Study (NBHS) showed that 88% of LBW patients with germinal matrix or IVH had normal cognitive outcomes (Whitaker) at 6 years.

Nevertheless, several analyses have reported abnormal neonatal CUS to be "significantly associated with" adverse long-term neurodevelopmental outcomes in ELBW cohorts. For instance, Mikkola found an association of abnormal CUS with CP and IQ at 5 years (Mikkola), and Taylor found an association of abnormal CUS with executive function and memory on the NEPSY (Taylor). However, the definition of CUS "abnormality" varies among studies, with some analyses including markers of white matter injury (PVL or ventricular enlargement (VE)) and others limiting only to IVH. In addition, a finding of association does not specifically address the independent *predictive* power of neonatal CUS, particularly with respect to cognitive outcome in later childhood. In fact, Hack, et. al. demonstrated that only 36% of those with a Mental Processing Composite (MPC) of <85 at 8 years had had an abnormal CUS, and only 45% of those with MPC<70 (Hack #3). In the 6-year follow-up of the NBHS cohort, only 12% of those with GM/IVH had borderline IQ or mental retardation (Whitaker). In that study, PVL/VE was separately assessed; this revealed a stronger 56.5% of those with PVL/VE had borderline IQ or mental retardation. This may be a clinical insight to the importance of white matter (WM) injury for longer-term adverse outcomes *including cognitive outcomes*. Nevertheless, more that 40% of patients with PVL/VE had normal intelligence at 6 years - a finding, which, in turn, may serve to underscore the inability of routine CUS to see anything more subtle than the most definitive WM injury.

Other potential predictors of long-term neurodevelopmental outcome:

Investigators have attempted to determine other, more reliable predictors of longer-term outcomes of preterm infants. Doyle reported on prediction of survival free of major disability at 5 years among the surviving VICS cohort on the basis of the *number of adverse neonatal variables* experienced by the child (Doyle #2). Although observed and predicted values were similar, the outcome was not specifically focused (i.e., combined neurologic/neurosensory/cognitive endpoint), the observed 95% CI range was broad for 2 and 3 variable groups, and the patient numbers were quite small. Others have assessed the predictive value of *earlier neurodevelopmental findings*. Marlow found that only severe

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disability at 30 months was highly predictive of 6-year outcome; 38% of children defined as mild or moderately disabled and 24% with "no disabilities" had moderate or severe disabilities at 6 years. Hack (#3) found the positive predictive value of MDI<70 at 20 months for MPC<70 at 8 years to be extremely poor (PPV=0.37). However, some intriguing links between neonatal brain injury and longitudinal decline in cognitive ability have been reported. In follow-up to the I-IVHP trial, Ment found that cognitive scores declined from 36 to 96 months only in the subset of patients with early IVH coupled with PVL or VE (Ment). Also from the I-IVHP trial, the presence of spastic cerebral palsy at 3 years was more strongly predictive of IQ<70 at 8 years than was cognitive testing at 3 years (Pleacher). These findings are interesting, but perhaps not surprising, in light of the proposed mechanism linking white matter injury with reduced connectivity, gray matter loss, and cognitive delay (Boardman, Inder).

Summary: Aggregate abnormal findings on neonatal CUS do not reliably predict either short- or long-term neurodevelopmental outcomes, although markers of WM injury appear to be stronger links. Early cognitive measures also do not predict later cognitive outcome well in most circumstances. These findings emphasize the deficits of routine CUS to detect subtle injury, and also underscore the poor predictive validity of early cognitive measures for later cognitive outcomes (Aylward). These findings also suggest that better delineation of neonatal WM injury may enhance efforts to predict outcomes.

MRI: Delineation of injury and predicting outcomes

Imaging brain injury:

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Studies comparing the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period have shown that MRI detects white matter injury better than CUS (Maaloof, Childs), and provides additional information on brain development not noted by cranial US. Studies have also demonstrated that subtle and diffuse WM injury, not detectable by CUS, may be common among preterm infants at term (Counsell).

White matter injury and cognitive outcome:

Cognitive delay is a significant impairment and difficult to predict. Recent studies have demonstrated that WM injury in the preterm infant is associated with both reduced cortical gray matter volume, and with reduced deep gray matter volume by MRI at term equivalent age (Inder, Boardman). There are several potential mechanistic pathways, including via direct axonal or subplate neuron injury that may explain this finding. The common endpoint is reduced connectivity, limited neuronal differentiation, and poor cognitive outcome. In fact, recent research using MRI tractography in a series of former preterm infants at approximately 2 years of age has provided at least proof of concept for this theory of reduced cortical and thalamic connections after WM injury (#2 Counsell).

Brain and WM injury by MRI and executive and behavioral outcomes in preterm infants:

Extremely low birth weight and very preterm infants have been reported to be at greater risk for executive dysfunction, as well as emotional and behavioral problems at 2 years, 4 years and at school age (#2 Anderson, Woodward #1, Taylor). These problems are infrequently the focus of neurodevelopmental outcomes studies, and are considered by some to be less serious than cognitive impairment. However, impairments across these domains have substantial impact on academic achievement, follow-up needs, and family

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interactions. Recent studies have suggested that these impairments may be associated with specific brain injury types and patterns among preterm children. In a brain diffusion tensor imaging (DTI) MRI study of preterm and term adolescents, Skranes, et. al. (Skranes) demonstrated that the preterm group were more likely to have attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) diagnoses or symptoms. Those with ADHD and ASD had lower fractional anisotropy (FA) in many WM areas, consistent with WM injury and impaired WM connectivity throughout the brain. Recent analyses have also demonstrated that WM injury on near-term MRI may predict executive and behavioral problems among preterm infant in early childhood. In a single center study, abnormal near-term MRI in VLBW infants was associated with positive M-CHAT screen in early childhood (Limperopoulos). Impaired working memory performance (Woodward #2) and self-regulation (Clark) at 2 years have both been associated with moderate-severe WM injury on near-term MRI. Specific regional injury patterns have furthermore been associated with working memory deficits.

MRI in preterm infants and early neurodevelopmental outcome

After early studies suggesting that MRI at near term was a more powerful predictive tool than CUS for short-term neurodevelopmental outcome (Valkama, Roelents-van-Rijn, Mirmiran), larger MRI studies were undertaken. Many have been single-center efforts, focused chiefly on the association of early neurodevelopmental outcomes with MRI findings in preterm infants at term and earlier, and without extensive comparison of the predictive validity of MRI and CUS. Among these, Miller, et. al. (UCSF, <34 weeks EGA, 86 survivors) and Dyet, et. al. (Hammersmith, <30 weeks EGA, 119 survivors) described MRI findings from birth through near-term and found that WM injury, particularly diffuse injury, was common and was associated with adverse neurodevelopmental outcomes. Recent evidence has also suggested that WM injury on neonatal MRI predicted motor developmental delays at 1 year corrected age with high specificity among very preterm infants (Spittle). Cerebellar injury, not easily seen with routine CUS, was also a prognostic indicator of poor outcome. Of importance, although MRI data were meticulously obtained, only 66% of the group had complete follow-up information.

However, other groups have preterm MRI cohorts, with research aims that include comparison of predictive capabilities of MRI and CUS.

- The 2-year neurodevelopmental outcomes of the New Zealand (NZ) cohort (Woodward #3) (<30 weeks EGA, 167 survivors) revealed that 1) presence of moderate-severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) although increasing severity of WM injury was associated with worse Bayley MDI scores, an independent association of moderate-severe WM injury with severe cognitive delay was not reached. Although sensitivity of moderate-severe WM to predict CP (65%), neurosensory impairment (82%) and severe cognitive delay (41%) was improved over abnormalities on CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n=29) or severe (n=6) WM injury was small, and approximately half of those did not have neurodevelopmental impairment.
- The 2-year results of the Australian cohort (<1250 g or <30 weeks EGA, n=221) (Hunt) showed "major" white matter injury to be a more significant independent risk factor than PVL for CP. Major WM injury was found to be an independent risk factor for

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neurosensory disability where PVL was not. IVH grade 4 was not found to be a significant risk factor for either outcome.

- **SUPPORT Neuroimaging and Neurodevelopmental Outcomes cohort:** The birth date of the first enrolled patient was 5/10/05. Enrollment was completed with SUPPORT main trial in February 2009, and follow-up at 18-22 months is ongoing.

SUPPORT Neuroimaging cohort: Unique and valuable

The SUPPORT Neuroimaging cohort, comprised of ~530 extremely preterm infants surviving to near-term with complete CUS and MRI neuroimaging will be the largest preterm brain MRI cohort worldwide with comprehensive early childhood follow-up. This cohort is also a higher-risk group than other cohorts, and thus targets one of the most important outcomes groups. The SUPPORT Neuroimaging cohort is inherently exceptional due to its development within a randomized controlled trial. Thus, the management profile of a crucial neonatal care component has been more carefully controlled and monitored than would otherwise be the case. This also allows for secondary analyses of the association of respiratory management strategies with subtle MRI findings and with outcomes. The SUPPORT Neuroimaging cohort also has a number of advantages over other preterm/MRI cohorts:

1) New Zealand (NZ) cohort:
    a. Setting: SUPPORT: Embedded in a randomized controlled trial within a multicenter network with focused neurodevelopmental follow-up priorities; NZ: two centers one in New Zealand another in Melbourne, Australia, with a primary focus on MRI imaging
    b. EGA/risk profile:
        i. SUPPORT: <28 weeks EGA; NZ cohort: <30 weeks. In the NZ cohort, only 87/167 were <1000 g BW, and 95/167 were <28 weeks.
    c. Cohort size: SUPPORT: ~530 survivors to near-term; NZ: 167 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. SUPPORT: Two CUS required by the study protocol at specific times (4-14 days and near-term); NZ: number and timing of CUS not required as part of study protocol, but reported CUS usually obtained within 2 days, 5-7 days, 4-6 weeks; if "abnormality" detected, more frequently performed.
        ii. SUPPORT: central reader, detailed data collection; NZ: No central reader. "Worst" CUS findings recorded only related respect to PVL/echolucency, grade 3 or 4 IVH
    e. Timing/interpretation of MRI:
        i. BOTH: Near-term
        ii. BOTH: Central reader
        iii. SUPPORT: detailed MRI central reader data collection form; NZ: central reader data collection instrument not known, but MRI abnormality categories broad.
    f. Non-imaging data collection:
        i. SUPPORT: extensive, including detailed respiratory data; NZ: less detailed
2) Australia cohort:
    a. Setting: Single center in Melbourne, Australia

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b. EGA/risk profile:
    i. <30 weeks, <1250 g.
c. Cohort size: 221 survivors at 2 years.
d. Timing/interpretation of CUS:
    i. Not required, retrospectively gathered data (communication, Rod Hunt).
    ii. "Worst" CUS findings gathered - PVL, grade 4 IVH
e. Timing/interpretation of MRI:
    i. Near-term
    ii. Central reader
f. Non-imaging data collection:
    i. Routine

3) Hammersmith cohort:
    a. Setting: Single center
    b. EGA/risk profile:
        i. <30 weeks.
    c. Cohort size: 119 survivors at 2 years. **Note: complete follow-up data were available for only 66% of the group**
    d. Timing/interpretation of CUS:
        i. CUS not focus – studies thus far report MRI
    e. Timing/interpretation of MRI:
        i. MRI serial – from birth to near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
4) UCSF:
    a. Small, single center
    b. <34 weeks
    c. 86 survivors at 2 years
    d. CUS not focus – MRI's serial from birth to near-term
    e. Non-imaging data routine

Summary: MRI is better than CUS in identifying subtle and diffuse white matter injury, which is relatively common among preterm infants at term, as well as cerebellar, and gray matter abnormalities. Early small and single-center studies suggested that MRI better predicts adverse neuromotor outcome than CUS. Two-year results of the NZ cohort have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities, but not with adverse cognitive outcome. The extent to which these findings will be enhanced and clarified, and how or when MRI should be applied in routine clinical practice, awaits the 18-22 month follow-up results of the larger, higher-risk SUPPORT Neuroimaging cohort. However, a biologic mechanism exists for the link between WM injury and cognitive impairment. Early neurodevelopmental findings are poor predictors of later challenges, but subtle neonatal WM abnormalities by MRI may predict cognitive, behavioral, and executive function impairments at school-age that cannot be delineated at 18-22 months.

Later outcomes: Need for SUPPORT Neuroimaging extended follow-up

Evidence for altered brain development: Corroboration of need for long-term follow-up

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Short-term neurodevelopmental outcomes are only a tiny window into the future of a former preterm child. Difficulties in cognition, performance, verbal/language skills, attention and behavior may not be delineated until later ages. There are also data to support the concept that even minor, undiagnosed brain injury sustained preterm infant is associated with disordered brain development. Rademaker, et. al. found that even minor differences in lesion severity on MRI performed at 8 years of age in <32 week EGA appeared more accurate in prediction of IQ and total impairment score than neonatal CUS (Rademaker). These findings may suggest that subtle injury could have been seen on *neonatal* MRI, which in turn, could have aided in prediction. In a DTI and volumetric MRI study, Yung demonstrated that *neurologically normal* LBW preterm infants at 8-12 years had significantly reduced WM volumes than term controls, and that this was significantly related to reduced IQ (Yung). This finding again suggests that early WM injury leading to reduced volume may have been identifiable on neonatal MRI. Kesler, et. al. described high-resolution MRI results from 73 preterm and 33 term infants at 7-11 years of age; preterm infants had disorganized cortical development, potentially involving disrupted neural migration (Kesler).

Importance of SUPPORT Neuroimaging secondary long-term follow-up

- Our current ability to predict later childhood outcomes from perinatal and neonatal variables is limited. The prognostic validity of neonatal CUS findings is limited, particularly for cognitive outcomes. Even early childhood neurodevelopmental outcome, apart from severe impairment, do not accurately predict later childhood neurocognitive outcome. MRI holds promise as a better predictive modality, but neonatal MRI has not been evaluated on a large scale with respect to long-term, school-age outcomes.
- Performance skills are different at 18-22 months than 6½ - 7½ years. Assessments at the later age may uncover subtle, yet significant problems, including attention/behavior problems, language and verbal delays, and academic impairment, which may be predicted by neonatal WM brain injury seen by MRI.
- The SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary was designed with MRI/CUS predictive comparison in mind.
- 18-22 month follow-up is already part of this secondary study. Thus, there is a crucial and rare opportunity to evaluate longitudinal neurodevelopmental changes, and importantly, how neonatal brain injury patterns and other variables may be associated with changes in cognitive or functional outcomes over time.
- This is a prospectively enrolled secondary cohort, embedded within SUPPORT RCT. These patients have therefore had a more consistent respiratory management approach, and comprehensive respiratory data collection. This provides a unique opportunity for analyses of randomized ventilation/oxygenation arms of Neuroimaging cohort outcomes at 6½ - 7½ years.
- Neurodevelopmental follow-up is already a focused objective of the NICHD NRN, and extended 6-7 year follow-up has recently been undertaken for a previous trial (Shankaran). In developing this SUPPORT Neuroimaging school-age follow-up protocol, we have been able to utilize experience gained from the challenges faced during the previous extended follow-up project.
- Other preterm/MRI cohorts, notably the NZ cohort, already have moved forward with longer-term follow-up (Clark, Woodward #1).

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III) STUDY DESIGN:

Objective: This is a prospective, extended follow-up study of 6½ - 7½ year neurodevelopmental outcomes of the SUPPORT Neuroimaging Secondary cohort. We will evaluate and compare the capabilities of *neonatal neuroimaging* - CUS and near-term MRI – to predict cognitive impairment, disability, and neuromotor impairment at 6½ - 7½ years. We will evaluate longitudinal changes in neurodevelopmental outcome, and assess associated neuroimaging findings and other variables. We will also determine if ventilatory or oxygenation saturation SUPPORT interventions are associated with differences in 6½ - 7½ year neurodevelopmental outcomes.

Outcomes:

- Primary:
  - IQ by WISC-IV<70 or death after discharge
- Secondary:
  - IQ score (continuous) by WISC-IV among survivors
  - Disability
    - Severe: Any of: WISC-IV>3 SD below mean, severely impaired neuromotor/functional outcome (non-ambulatory, GMFCS level 4-5), profound hearing loss or blindness (not functionally correctable),
    - Moderate: Any of: WISC-IV2-3 SD below mean, moderately impaired neuromotor/functional outcome
    - Mild: Any of: WISC-IV1-2 SD below mean, mildly impaired neuromotor/functional outcome (abnormal neurologic exam, but walking independently, GMFCS level 1-2)
  - Neuromotor, movement
    - Cerebral palsy, classified anatomically and functionally according to Definition and Classification of Cerebral Palsy, February 2007 guidelines (Baxter) ; Motor and coordination impairment, as determined by administration of the Movement Assessment Battery for Children, version 2 (M-ABC-2) (Burns, Smits-Engelsman).
  - Mild-moderate cognitive impairment (WISC-IV 1-2 SD below mean), severe cognitive impairment (WISC-IV 2-3 SD below mean), and profound cognitive impairment (WISC-IV>3 SD below mean)
  - Executive function and achievement delays (evaluated by NEPSY-II subtests; Behavior Rating Inventory of Executive Function (BRIEF, parent form) (Roze); Woodcock-Johnson III subtests (Taylor))
  - Behavioral and attention deficits (evaluated by Strengths and Difficulties Questionnaire (SDQ) (Goodman, Muris); Conners' Rating Scale (ADHD short form only); Social Communication Questionnaire (SCQ) (Chandler, Eaves))
  - Chronic conditions and health-related quality of life concerns (evaluated by the Questionnaire for Identifying Children with Chronic Conditions – revised (QUICCC-R) (Stein); the Pediatric Quality of Life Inventory (Peds QL) (Majnemer))

Study population:

- The study population (SUPPORT Neuroimaging cohort) will be comprised of the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary enrollees

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who survived to discharge, with complete neuroimaging. **It is estimated that approximately 530 patients meet these criteria.**

- As described in the SUPPORT Neuroimaging and Neurodevelopmental outcome secondary, these patients will have had two CUS (early: 4-14 days of age; late: 35-42 weeks and within 5 days of MRI) and a brain MRI at 35-42 weeks.
    - The CUS with the most severe abnormalities (the "worst" CUS) will be used in comparative analyses
- Estimated cohort size at the time of neurodevelopmental follow-up
    - Follow-up at 18-22 months (ongoing)
        - Estimate 3% death after discharge, 10% loss to F-U:
            - **Cohort=~460 patients**
    - Follow-up at 6½ - 7½ years
        - Estimate additional 20% loss to follow-up:
            - **Cohort = 370 patients**

Design:

- This study is a long-term cognitive, neuromotor, functional, executive function, behavioral assessment of the SUPPORT Neuroimaging cohort at school age (6 ½ - 7 ½ years). **No further neuroimaging is being proposed**.
- Visit at 6½ - 7½ years:
    - The visit battery was assembled and revised after extensive discussions with Protocol Review Subcommittee, Extended SUPPORT Neuroimaging and Neurodevelopmental Outcomes Subcommittee, external advisory reviewers, NRN Follow-up PI group, NRN site psychologists, and evaluation of the challenges and successes of the Extended Hypothermia Follow-up study. The following issues were particularly addressed:
        - Length of visit: Tests and questionnaires were chosen to balance the need for robust neurodevelopmental evaluation, but remain within the confines of a reasonable academic study visit period.
        - Age at visit: Due to differences in age at school start across the U.S., as well as the fact that the WISC-IV "floor" is at 6 years 0 months, there was strong concern that a 6-7 year window would be suboptimal. Therefore, the follow-up window for this study is 6 ½ - 7 ½ years, which will hopefully ameliorate the potential for insufficient sensitivity of WISC-IV for low functioning children at very young ages, and allow for more consistent school exposure across the cohort.
        - Language for tests and questionnaires: There was consensus that tests and questionnaires should be available and normed in Spanish, particularly the instrument used for the cognitive evaluation (primary outcome). It is noted that the NEPSY-II is not available in Spanish. However, site "credit" for a visit will not be linked to attempt of the NEPSY-II in the case of Spanish-speaking children. Furthermore, the BRIEF (parent questionnaire) is available in Spanish, providing some input on the child's executive function.
    - Following is the test and questionnaire grid; note that the child testing and parent questionnaires can be administered simultaneously. Furthermore, the "Break" as presented is a suggested timing. It is understood that each child is an individual, and the NRN site psychologist will determine timing and number of breaks throughout the visit for that particular child's needs.

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CHILD ASSESSMENTS

Test/questionnaire	**Estimated time AGE RANGE**	**Spanish version? Links to product sites**
ASSESSMENTS		
Check in: Wt, Ht, HC	~10 min	
WISC-IV *	~45-60 min **6 yr 0 months – 16 yr 11 months**	YES http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&Mode=detail&Leaf=avpproducts
Movement-ABC –II *Manual dexterity, Aiming and Catching, Balance*	20-30 min **3-12 years**	Interpreter if needed http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308
Woodcock-Johnson III (ACH) Letter-Word Identification Calculation	~15 minutes **2 years -90+ years**	YES = "Bateria III" http://www.riverpub.com/products; http://www.riverpub.com/products/wjIIIAchievement/details.html
BREAK		
NEPSY II subtests *Executive function domain* Auditory Attention/Response set Inhibition *Visuospatial domain* Design Copying Arrows *Memory* Memory for Names	~25 min **Auditory Attention/Response (5-16 yrs); Inhibition (5-12); Design copying (3-16); Arrows (5-16); Memory for names (5-16)**	No
Neurologic exam (for cerebral palsy)	~15 min	Interpreter if needed
Functional *GMFCS* *Bimanual Fine Motor Function*	5 min **GMFCS – 6-12 yr BFMF – 4 yrs and older**	Interpreter if needed; http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf

- * Pediatric Evaluation of Disability Inventory (PEDI)*
  - For children unable to be tested by the WISC-IV due to severe neurodevelopmental impairment, the PEDI will be administered.

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PARENT QUESTIONNAIRES

Test/questionnaire	Estimated time AGE RANGE	Spanish version? Links to product site
PARENT QUESTIONNAIRES		
Medical history/SES/living arrangement	15 min	Interpreter if needed
QUICCC-R	5-10 min **2-18 years**	YES; http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF
PedsQL (Parent)	5-10 min **versions - 2-4, 5-7, 8-12, 13-18 yrs**	YES; http://www.pedsql.org/
Strengths and Difficulties Questionnaire (SDQ) (Parent)	5-10 min **4-10 yrs**	YES; http://www.sdqinfo.com/
Conners Rating Scale (Parent) (ADHD or Short form only)	10 min **6 yr-17 yr 11 months**	YES; http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&Mode=scoring&Leaf=Conners_3_SF#3
Social Communication Questionnaire (Parent; Lifetime form)	10 min **Over 4 years**	YES; http://portal.wpspublish.com/portal/page?_pageid=53,70432&_dad=portal&_schema=PORTAL
Behavior Rating Inventory of Executive Function (BRIEF-Parent version)	15 min **5-18 yrs**	YES; http://www3.parinc.com/products/product.aspx?Productid=BRIEF

Statistical considerations:

Analyses:

- Since we are concerned with the relative diagnostic power of the MRI versus the CUS, an appropriate statistical methodology is an ROC analysis. This analysis is based on the sensitivity and specificity and compares the diagnostic power over the entire range of the diagnostic variable(s) and thus negates the need to select "cut points". The analysis related to the primary hypothesis will compare the ROC curves for a predictive model based on the MRI data versus a predictive model based on the CUS data. The WISC-IV < 70 or death after discharge will be the primary outcome variable. The WISC-IV < 70 among survivors will also be evaluated as an outcome variable.
    - We will conduct the ROC analysis with WISC-IV <70 (or death after discharge) as the outcome when either MRI or CUS data are in the predictive model and will compare the ROCs for the two models for statistical significance. Since MRI and CUS are done on the same subjects, it will not be necessary to adjust for risk factors in comparing the two tools.
        - In separate analyses, NRN center may be entered as a variable to assess the confounding effects of site. Although CUS and MRI are

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centrally-read, and significant attempts to ensure reliability and consistency of WPPSI evaluation across sites will be made, unanticipated and unmeasurable differences between sites in quality of neuroimaging or in WISC-IV administration *may* confound analyses;

- We will conduct the ROC analysis with WISC-IV <70 (or death after discharge) as the outcome when only "traditional variables" (non-neuroimaging variables) are the only variables in the model;
- We will also do the ROC analysis that compares the contribution of MRI and CUS to the prediction of outcome above and beyond that of the traditional clinical variables.
- Will also do the ROC analysis that compares the incremental value of adding MRI to the prediction of outcome above and beyond that of traditional clinical variables plus CUS
- Logistic regression analysis will be used to compare 6½ - 7½ year neurodevelopmental outcomes (or death after discharge) between oxygenation and ventilation SUPPORT randomized groups. These analyses will be adjusted for baseline risk variables.
  - The baseline risk variables pre-specified for adjustment in the main SUPPORT trial are the stratification variables (NRN site and GA group). In comparing 6½ - 7½ year outcomes between SUPPORT randomized groups, we plan to adjust only for these variables in our initial approach. However, since the Neuroimaging cohort may not be representative of the originally randomized study cohort, we will investigate differences between the 6½ - 7½ year follow-up groups and consider a subsequent level analysis adding other factors if there is an indication of systematic differences.
- Local vs. central neuroimaging secondary analyses: As recommended by the Protocol Review Subcommittee, secondary analyses including evaluation of local MRI reading will be undertaken.
  - Local CUS readings are already collected in the SUPPORT or GDB database; local MRI readings (print-out of final local read with study ID and center written on the document, but patient identifiers removed or blacked out) will be collected.
  - Accuracy of local compared with central neuroimaging interpretation will be performed by sensitivity and specificity analyses (Hintz #3).
  - Additional analyses will compare capability of local MRI read and central MRI read to predict 6½ - 7½ year outcomes by ROC analysis.

- "Traditional non-neuroimaging variables": Based on previous investigations assessing the associations of demographic, socioeconomic, perinatal, and neonatal factors with school-age outcomes (Taylor, Doyle #2), we propose the following non-neuroimaging variables will be used in model development; other variables may be considered.
  - Center
  - Gestational age
  - Race
  - Gender
  - Multiple gestation
  - Maternal education level (at baseline)

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- [SUPPORT treatment group]
- Sepsis or meningitis
- NEC
- BPD
- Postnatal steroids
- ROP stage III or more severe
- Length of initial hospital stay (EGA adjusted, i.e., PCA at discharge)
- Any surgery during initial hospitalization

Sample size and power analysis (Primary Hypothesis):

- The sample sizes in the table below are based on formulae for two correlated ROCs (e.g. two ROCs based on the same sample). According to the discussion in the protocol above, we assume that around 370 infants will be available for the 6½ - 7½ year IQ evaluation, assuming ~20% loss to follow-up between 18-22 months and school-age. For a two-tailed test at the 0.05 level of significance and assuming the lowest area under the ROC curve (AUC) for the MRI and the CUS is 75%, an even more conservative estimate of 350 children would produce the powers in the table below for an array of detectable increases in the AUC and prevalence of outcome.

POWER FOR SELECTED INCREASES FROM 75% IN THE AUC OF THE ROC AND PREVALENCES OF THE PRIMARY OUTCOME:
SAMPLE SIZE = 350

AUC Inc. / Outcome P	5%	6%	7%	8%	9%	10%
20%	31%	43%	55%	67%	77%	86%
25%	37%	50%	64%	76%	85%	92%
30%	42%	56%	70%	81%	90%	95%

Hence, if the prevalence of the primary outcome is as low as 20% a conservative sample size of 350 would identify an AUC increase of 10% with reasonable power (86%); if the prevalence is 30%, the detectable increase would be 8% (with power 80%).

Budget: The costs of this proposed follow-up study would span over several years. The first enrolled patient will reach the 6th birthday on 05/10/2011, thus the first window will open 11/10/2011. **It is estimated that 6½ - 7½ year follow-up windows will extend from November 2011 to late 2016.** A range of costs for some subcategories has been provided for loss to follow-up rates between 18-22 months to 6 ½ - 7 ½ years of 10% - 20%.

- Tracking: Similar to the Extended Follow-up of the Hypothermia Trial, tracking will be critical to ensure the best possible follow-up. **Tracking tools and forms have already been developed and launched. RTI is sending tracking reminders to sites.** Because of the importance robust school-age follow-up rates, considerable

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funds have been budgeted for tracking contacts. The following are suggested contact schedules, although each site will implement specific tracking and contacts appropriate for their patients:
  - Between 18-22 month and 3-4 years: <u>at least</u> 2 phone or other family contacts/ tracking events
  - Between 3-4 years and 6½ - 7½ years: <u>at least</u> 4 phone or other family contacts/ tracking events
  - **$420 per child has been budgeted for tracking.** Release of tracking funds will be contingent on completion of the SEF01 form (tracking form for 18-22 month to 3-4 year contacts).
  - **Total: $155,400 – $174,300**
- <u>Consents</u>: Consent to contact families for possible 6½ - 7½ year follow-up is currently being sought at the 18-22 month visit. Tracking will then commence as noted above. Formal signed consent will be obtained for the majority of the cohort at the time of the 6½ - 7½ year follow-up visit. It is expected that the consent process will take ~1/2 hour (@$35/hour).
  - 14 patients had already been seen in 18-22 month follow-up prior to Dr. Higgins' announcement to NRN site PI's and Follow-up PI's to request to maintain contact. These patients will require some additional time for tracking/consent. We expect that the consent process will take ~1 hour in these cases (@$35/hour).
  - **Total: $6475-$7263**
- <u>Local MRI read:</u> We estimate that relatively little time (~1/2 hour per MRI x $35/hour) will be required to print out/copy final local MRI report, black out patient identifiers, and write in Center number and subject number. These documents will then be sent to RTI.
  - **Total: $9275**
- <u>Training and assuring reliability:</u> The first enrolled SUPPORT Neuroimaging cohort patient will reach the extended follow-up window opening in November 2011. However, there are just 10 patients in the first "wave" with the majority of patient windows not opening until February 2012. Furthermore, given the length of the SUPPORT trial, the final enrolled patients will have 6½ - 7½ year follow-up windows that extend to late 2016. Thus, the total cohort follow-up period will span approximately 5 years. To ensure ongoing training and achieve the best possible reliability for the primary outcome measure (WISC-IV), the following training and reliability assessments have been determined:
  - Training sessions: We propose adding another WISC-IV training session for all sites midway through the follow-up (late 2013 or early 2014). As with the Extended Hypothermia Follow-up, these training sessions will also include training in other components of the follow-up exam, including the NEPSY-II and PEDI. 15 sites are participating in the SUPPORT Neuroimaging secondary, but the 15th site (Emory) will not have patients reaching the 6th birthday until after 2013. We have also added incrementally to the cost per site in 2013 to adjust for inflation.
    - First training session (Fall 2011): $3200 x 14 sites =$44,800
    - Second training session (late 2013): $3400 x 15 sites =$51,000
  - Reliability assessment: In response to Protocol Review Subcommittee comments, we propose ongoing routine exam taping to be sent from

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participating sites to one of two GOLD STANDARD WISC-IV psychologists. After training and subsequent certification by one taped exam on a non-study patient, the first 3 exams from each site be taped and sent for review and comment, then approximately every 10th exam. This approach will necessitate a DVD recorder to be purchased by each site. We estimate that 3 hours will be required to review and comment upon each WISC-IV exam at $60/hour. Gold standard psychologists will assure that turn-around for comments on these exams be rapid so that sites can incorporate feedback in subsequent scheduled patients' visits. Thus, the budget would reflect the following:

- DVD recorders for each site: $350 x 15 sites = $5250
- Review and comment on certification exam =
  - 1 x 15 sites x 3 hours x $60/hr = $2700
- Review 1st 3 exams from each site =
  - 3x15 site x 3 hrs x $60/hr = $8100
- Review of every 10th exam: Dependent on follow-up numbers:
  - Approximately 30 additional exams x 3 hrs x $60/hr = $5400

- **Total = $117,250**

- 6½ - 7½ year visit costs:
  - $1200 per child has been budgeted for the study visit
  - **Total = $444,000-$498,000**

TOTAL BUDGET ESTIMATE: $732,400 - $806,088 *plus RTI costs*

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From: Susan Hintz
To: Yao, Qing
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Abstracts - SUPPORT and Hypothermia neuroimaging
Date: Sunday, October 11, 2009 10:44:38 AM

Thanks Qing! I will probably be getting back to you the week of October 19th with some outlines since I will be on clinical service in the intensive care unit for the next week.

Thanks

Susan

On Oct 6, 2009, at 7:41 AM, "Yao, Qing" <qyao@rti.org> wrote:

> Yes, I am ready. Please feel free to send me any requests. Thanks, -Qing
>
> ---
>
> **From:** Das, Abhik
> **Sent:** Tuesday, October 06, 2009 9:31 AM
> **To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Susan Hintz'
> **Subject:** RE: Abstracts - SUPPORT and Hypothermia neuroimaging
>
> I agree. Qing has already been assigned to work with Susan on this study.
>
> Thanks
>
> Abhik
>
> ---
>
> **From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, October 02, 2009 4:23 PM
> **To:** 'Susan Hintz'
> **Cc:** Das, Abhik
> **Subject:** RE: Abstracts - SUPPORT and Hypothermia neuroimaging
>
> Susan
> Sorry for the delay in response. I have been busy today.
>
> Your protocol states:
>
> **Outcomes**:
> Primary outcomes include
> • Death/Grade 3/4 IVH on 4-14 day cranial US
> • Death/Grade 3/4 IVH on 35-42 week cranial US
> • Death/PVL on 35-42 week cranial US
>
> This would definitely be of interest to folks at PAS as a late breaker, so I think (as long as Abhik has statistical help) this should be considered for a late breaker

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Rose

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thursday, October 01, 2009 5:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org
Subject: Abstracts - SUPPORT and Hypothermia neuroimaging

Hi Rose and Abhik

You both know that the cranial US readings for the SUPPORT neuroimaging cohort are almost done (the final CUS will be read by Tom in Detroit at the end of October). So, I think there will be time for analysis for those studies by late breaker deadline. This will be a unique group in that they are all <28 weeks, US have been obtained at specific times, they are centrally read, and perhaps most importantly, we will be able to report progression of abnormalities with respect to clinical factors and randomized SUPPORT treatment groups.

As you also know, we got delayed in the SUPPORT MRI readings delayed due to the Hypothermia readings. Although we are charging ahead and have already sent Kris back about 100+ completed MRI's, the SUPPORT MRI readings are very complex and very time-intensive. As Abhik has said, it may be difficult if not impossible to get all reading done and analysis done for an abstract by February 24. Don't get me wrong - I am still pushing to make it. Pat and I have been meeting at all hours to read, and I have 6:30 am MRI reading times booked with Pat 3x/week! But, I am suggesting that the analysis may be quite complicated, and we should also be thinking about cranial US analysis as a separate abstract. **Rose, do you think the cranial US analysis would be a valuable PAS late breaker on its own?**

The Hypothermia MRI's analysis should definitely be planned for late breaker - this is important, more detailed MRI information than has been previously reported, and I think could go a long way toward better characterizing potential injury pattern differences in cooled vs non-cooled babies. The neonatology community will be excited to hear this valuable information!

Just sharing my thoughts at the moment - thanks. Input welcomed!

Susan

--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]; Reubens, Linda; Jensen, Rosemary
Cc: mgfuller@ucsd.edu
Subject: RE: SUPPORT ROP queries Center 21 09OCT09
Date: Saturday, October 10, 2009 9:13:48 PM

We will address. I'm quite curious about this since I thought we were all clean years ago.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 2:10 PM
To: Phelps, Dale; Reubens, Linda; Jensen, Rosemary
Cc: mgfuller@ucsd.edu
Subject: SUPPORT ROP queries Center 21 09OCT09

We have a SUPPORT ROP query

thanks
Rose

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Michael Cotten"; Gloria Siaw; "Ronald N Goldberg"; "Gantz, Marie"
Subject: Re: SUPPORT ROP queries Center 19 09OCT09
Date: Friday, October 09, 2009 6:40:08 PM
Attachments: SUPPORT ROP queries Center 19 09OCT09.rtf

Rose
Here are the responses to your ROP queries. Let me know if there is anything else that you need.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b) (6)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/09/2009 05:09 PM

To "'Michael Cotten'" <cotte010@mc.duke.edu>, "'Ronald N Goldberg'" <goldb008@mc.duke.edu>, Gloria Siaw <gloria.siaw@duke.edu>, Kimberley A Fisher <kimberley.fisher@duke.edu>
cc "'Gantz, Marie'" <mgantz@rti.org>
Subject SUPPORT ROP queries Center 19 09OCT09

We have some ROP queries. Please try to address.

thanks
Rose[attachment "SUPPORT ROP queries Center 19 09OCT09.doc" deleted by Kimberley A Fisher/Pediatrics/mc/Duke]

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: NG03 has been corrected to reflect "no" for threshold. SUPP10 is correct. DMS has been updated.**	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: NG03 has been corrected to reflect "no" for threshold. SUPP10 is correct. DMS has been updated.**							**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: NG03 has been corrected to reflect "no" for threshold. SUPP10 is correct. DMS has been updated.**	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: NG03 has been corrected to reflect "no" for threshold. SUPP10 is correct. DMS has been updated.**							**Resolved**

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 1 but per SUPP10 highest stage in that zone was 1. **Resolution: NG03 has been updated to reflect zone 2 for reaching stage 2 in left eye. DMS has been updated.**	Per NG03 right eye reached ROP stage 2 in zone 1 but per SUPP10 highest stage in that zone was 1. **Resolution: NG03 has been updated to reflect zone 2 for reaching stage 2 in right DMS has been updated.**							**Resolved**

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0. **Resolution: Left eye stage 3 in zone 2 changed in GDB to reflect correction. DMS has been updated.**	Per NG03 right eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0. **Resolution: Right tage 3 in zone 2 changed in GDB to reflect correction. DMS has been updated**							**Resolved**

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1. **Resolution: NG03 highest stage is 1. DMS has been updated.**	Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1. **Resolution: NG03 should be stage 2 in zone 3. DMS has been updated.**							Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form. **Resolution: Exam (b) (6) left eye changed to "N" for threshold. DMS updated.**								Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: Threshold never reached. Changed on NG03 10/6/09.**	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10. **Resolution: Threshold never reached. Changed on NG03 10/6/09.**							Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: SUPP10 has been changed to reflect threshold on (b) (6) exam. DMSis updated.**								Resolved

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7
On SUPP10 exam dated (b) (6) 8 left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam on (b) (6) was entered in error and deleted. DMS updated.**	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam on (b) (6) was entered in error and deleted. DMS updated.**	Per SUPP10 infant had exam with mature vessels followed by an exam with stage 3 ROP in zone 1 (exams dated (b) (6) . **Resolution: Exam on (b) (6) was entered in error and deleted. DMS updated.**				

Query 8	Query resolution Center notes
	Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: ROP exam (b) (6) left eye marked "y" for Threshold. DMS updated.**	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: ROP exam (b) (6) rightmarked "y" for Threshold. DMS updated.**							Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams. **Resolution: NG03 was corrected to read NO for ROP. SUPP10 is correct. DMS has been updated.**								Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form. **Resolution: SUPP10 has been correct to reflect no threshold for left eye on exam (b) (6) DMShas been updated.**								Resolved

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
Multiple ROP exams were entered on SUPP10 for the same date(b) (6) **Resolution: Duplicate exam deleted. DMS updated.**	Multiple ROP exams were entered on SUPP10 for the same date (b) (6) **Resolution: Duplicate exam deleted. DMS updated.**	Multiple ROP exams were entered on SUPP10 for the same date (b) (6) **Resolution: Duplicate exam deleted. DMS updated.**						**Resolved**

Center ID number=19=Duke University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam for(b) (6) changed to "y" for threshold. DMS updated.**	On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam for (b) (6) changed to "y" for threshold. DMS updated.**	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam for(b) (6) changed to "y" for threshold. DMS updated.**	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam for (b) (6) changed to "y" for threshold. DMS updated.**

Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
				Resolved

Center ID number=19=Duke University Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam dated(b) (6) has been corrected to reflect threshold on left eye. DMS is updated.**								**Resolved**

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam(b) (6) corrected to reflect threshold on left eye. DMS updated.**	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form. **Resolution: Exam (b) (6) corrected to reflect threshold on right DMS updated.**							**Resolved**

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number(b) (6) Date of Birt(b) (6)

Query	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query Resolution Center Notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams. **Resolution: SUPP10 is correct. NG03 has been corrected to reflect no ROP. DMS has been updated.**								**Resolved**

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From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]; Nancy Peters
Cc: Gantz, Marie
Subject: RE: SUPPORT ROP queries Center 20 09OCT09
Date: Friday, October 09, 2009 5:20:20 PM

Nancy,
Let me know if you need help with this.
Mike

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 5:10 PM
To: Michael O`Shea; Nancy Peters
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 20 09OCT09

We have a few SUPPORT ROP Queries. We intend to lock the data set following transmission on 10/20.

thanks for all your help
Rose

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP queries Center 16 09OCT09
Date: Friday, October 09, 2009 5:14:45 PM

Thanks

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 4:06 PM
To: Wally Carlo, M.D.; Shirley Cosby; Vivien Phillips; Monica Collins
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 16 09OCT09

We have a few missing items and some queries for SUPPORT. Thanks for all your help!!!
Rose

16	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		FU window has closed but NF05 and NF09a have not been completed.

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT ROP queries Center 24 09OCT09
Date: Friday, October 09, 2009 5:12:00 PM

We have a few queries from SUPPORT (and one missing outcome).

thanks
rose
24 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Phelps, Dale"; "Reubens, Linda"; "Jensen, Rosemary"
Cc: "mgfuller@ucsd.edu"
Subject: SUPPORT ROP queries Center 21 09OCT09
Date: Friday, October 09, 2009 5:10:00 PM
Attachments: SUPPORT ROP queries Center 21 09OCT09.doc

We have a SUPPORT ROP query

thanks
Rose

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SUPPORT ROP Queries for Center 21-University of Rochester

Center ID number=21=University of Rochester Network number=(b) (6) Date of Birt(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Michael O`Shea"; "Nancy Peters"
Cc: "Gantz, Marie"
Subject: SUPPORT ROP queries Center 20 09OCT09
Date: Friday, October 09, 2009 5:09:00 PM
Attachments: SUPPORT ROP queries Center 20 09OCT09.doc

We have a few SUPPORT ROP Queries. We intend to lock the data set following transmission on 10/20.

thanks for all your help
Rose

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SUPPORT ROP Queries for Center 20-Wake Forest University

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.								

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.							

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From: Hensman, Angelita
To: Higgins, Rosemary (NIH/NICHD) [E]; Laptook, Abbot
Cc: "Gantz, Marie"
Subject: RE: SUPPORT ROP queries Center 14 09OCT09
Date: Friday, October 09, 2009 5:08:26 PM

These have been changed and edited numerous times. I will try to go over with Jenny on Tuesday and resolve before transmission.

Thanks

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 5:05 PM
To: Laptook, Abbot; Hensman, Angelita
Cc: 'Gantz, Marie'
Subject: SUPPORT ROP queries Center 14 09OCT09

Hi,
We are missing a few SUPPORT outcomes - The final date for data transmission is October 20.

thanks for all the help

Rose

14	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: ROP question
Date: Friday, October 09, 2009 4:50:15 PM
Attachments: SUPPORT ROP queries summary 09OCT09.doc
ROP queries 09OCT09.zip
Infants with missing outcomes 09OCT09.xls

Rose,

The ROP queries are attached, in the zipped file. I have also attached a summary of the queries and the usual missing data reminders for the week.

I am also about to re-run the cross-form queries so that the centers can be reminded for queries that are still outstanding. We will send those out on Monday.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 4:38 PM
To: Gantz, Marie; Finer, Neil; Wally Carlo
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: ROP question

NO, we can go with what we have – the manual states that we will determine status at 55 weeks, so we are likely to have many that we can't assign an outcome.

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 09, 2009 1:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: ROP question

Thanks, Rose. I will query those with "mature" eyes that still have ROP recorded. Do you think any queries are necessary for those who had two consecutive exams with vessels in zone 3 but still have ROP recorded in that eye?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 12:45 PM
To: Gantz, Marie; Finer, Neil; Wally Carlo
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: ROP question

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If an eye is "mature" the ROP should have resolved.

For the infants who still have a pending status at 55 weeks, if we have a normal exam subsequent to the 55 week exam, then we know that they did not have threshold ROP or surgery so could potentially be classified.

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 09, 2009 11:13 AM
To: Finer, Neil; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: ROP question

Hi all,

In response to my message below, Neil said that it might be an issue if infants who reached final status by having two exams with vessels in zone 3 still have ROP. So, I have summarized the cases where there was either an exam with mature vessels or two consecutive exams with vessels in zone 3 but the final exam still has some degree of ROP.

Infants with an exam with mature vessels that still show ROP in the "mature" eye:
Stage 1 ROP: 2
Stage 2 ROP: 2
Stage 3 ROP: 1

Infants with two consecutive exams with vessels in zone 3 where the last exam still shows ROP in that eye:
Stage 1 ROP: 54
Stage 2 ROP: 13
Stage 3 ROP: 6

Please let me know as soon as possible if any of these cases need to be queried. I can ask the centers to confirm that there was still ROP by entering an F5 on the SUPP10 and/or ask that they find out if there were subsequent exams with no ROP. The queries are basically ready to go out other than this final issue.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Gantz, Marie
Sent: Thursday, October 08, 2009 1:48 PM
To: 'Finer, Neil'; Wally Carlo; 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Das, Abhik; Rich, Wade; Zaterka-Baxter, Kristin
Subject: ROP question

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Hi all,

I am trying to finalize the ROP queries to go out this week and I have a question. If an infant meets our criteria for final ROP status by having two exams with vessels in zone 3, is it a problem if one of those exams also has stage 3 ROP? If it is, I can query cases we have that are like that.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Summary of ROP queries (can be >1 query per infant)

The FREQ Procedure

Query		
Query	Frequency	Cumulative Frequency
Multiple ROP exams were entered on SUPP10 for the same date.	13	13
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP.	6	19
Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP.	5	24
On SUPP10 exam left eye had mature vessels but also had ROP.	5	29
On SUPP10 exam right eye had mature vessels but also had ROP.	6	35
On SUPP10 exam highest ROP stage in lowest zone is > highest stage in any zone.	14	49
On SUPP10 exam lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo'	3	52
On SUPP10 exam left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	66	118
On SUPP10 exam right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	65	183
On SUPP10 exam left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	17	200
On SUPP10 exam right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	15	215
Per SUPP10 ROP reached stage 3 in one eye but only stage 1 or no ROP in the other eye.	7	222
Per SUPP10 surgery for ROP was performed in only one eye.	7	229
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP.	6	235
Per SUPP10 one or both eyes went from stage 2 or 3 ROP to mature within a week.	3	238
Per SUPP10 infant had exam with mature vessels followed by an exam with stage 3 ROP in zone 1.	1	239
Per SUPP10 infant had 2 exams with vessels in zone 3 followed by an exam with surgery for ROP.	1	240
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.	14	254
Per NG03 left eye reached a higher stage of ROP than is reported on the SUPP10 (pre-2006).	13	267
Per NG03 right eye reached a higher stage of ROP than is reported on the SUPP10 (pre-2006).	10	277
NG03 left eye exam results do not match any of the exams entered on SUPP10 (pre-2006).	1	278
NG03 right eye exam results do not match any of the exams entered on SUPP10 (pre-2006).	3	281
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10 (pre-2006).	4	285
Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10 (pre-2006).	4	289
Per NG03 left eye had surgery for ROP but that is not reflected on the SUPP10 (pre-2006).	1	290
Per NG03 surgery was performed for ROP but that is not reflected on the SUPP10.	2	292
Per NG03 stage 3 or worse ROP was diagnosed but that is not reflected on the SUPP10.	1	293
Per NG03 plus disease was diagnosed but that is not reflected on the SUPP10.	2	295
Per NG03 final ROP status was 2='severe ROP' but that is not reflected on the SUPP10.	1	296

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SUPPORT ROP Queries for Center 26-University of New Mexico

Center ID number=26=University of New Mexico Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated (b) (6) left eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	On SUPP10 exam dated (b) (6) left eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	On SUPP10 exam dated (b) (6) right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.					

Query resolution: Center notes

Center ID number=26=University of New Mexico Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo.'								

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SUPPORT ROP Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo.'								

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.								

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.								

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=3=Case Western University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.					

Query resolution: Center notes

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SUPPORT ROP Queries for Center 4-University of Texas-Dallas

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.								

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 one or both eyes went from stage 2 or 3 ROP to mature within a week. If this is correct, please F5 to confirm.	Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.							

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Query resolution: Center notes

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye reached ROP stage 1 in zone 2 but per SUPP10 highest stage in that zone was 0.								

Center ID number=4=University of Texas-Dallas Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.								

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SUPPORT ROP Queries for Center 4-University of Texas-Dallas

Center ID number=4=University of Texas-Dallas Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated(b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=4=University of Texas-Dallas Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6) .								

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SUPPORT ROP Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.								

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=5=Wayne State University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.								

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SUPPORT ROP Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.							

Center ID number=5=Wayne State University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.				

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SUPPORT ROP Queries for Center 8-University of Miami

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye had an exam with ROP stage 3 in zone 1 but that is not reflected on the SUPP10.								

Center ID number=8=University of Miami Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.								

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SUPPORT ROP Queries for Center 9-Emory University

Center ID number=9=Emory University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								

Center ID number=9=Emory University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								

Center ID number=9=Emory University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=9=Emory University Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 0. If this is correct, please F5 to confirm.								

Center ID number=9=Emory University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=9=Emory University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.					

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SUPPORT ROP Queries for Center 9-Emory University

Query resolution: Center notes

Center ID number=9=Emory University Network number (b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

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SUPPORT ROP Queries for Center 11-University of Cincinnati

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 1 in zone 3 but per SUPP10 highest stage in that zone was 0.								

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.	Per NG03 right eye had an exam with ROP stage 1 in zone 1 but that is not reflected on the SUPP10.							

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.	Per NG03 left eye had surgery for ROP but that is not reflected on the SUPP10.						

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 highest stage ROP reached in left eye was stage 0 and highest in right eye was stage 3. If this is correct, please F5 to confirm.							

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.								

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	On SUPP10 exam dated (b) (6) right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.							

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SUPPORT ROP Queries for Center 11-University of Cincinnati

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) highest ROP stage in lowest zone is > highest stage in any zone.								

Center ID number=11=University of Cincinnati Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated(b) (6) highest ROP stage in lowest zone is > highest stage in any zone.							

Center ID number=11=University of Cincinnati Network number=88111 Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=11=University of Cincinnati Network number=88451 Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) highest ROP stage in lowest zone is > highest stage in any zone.								

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SUPPORT ROP Queries for Center 12-Indiana University

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 1 in zone 3 but per SUPP10 highest stage in that zone was 0.								

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) lowest zone is '5=Post laser/cryo' but highest stage is not '6=Post laser/cryo.'								

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.								

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=12=Indiana University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.								

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SUPPORT ROP Queries for Center 13-Yale University

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 0 and highest in right eye was stage 3. If this is correct, please F5 to confirm.								

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query resolution: Center notes

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.							

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

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SUPPORT ROP Queries for Center 13: Yale University

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=13=Yale University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.							

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SUPPORT ROP Queries for Center 14-Brown University

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=14=Brown University Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) 8 right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

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SUPPORT ROP Queries for Center 14-Brown University

Center ID number=14=Brown University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=14=Brown University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	Per NG03 plus disease was diagnosed but that is not reflected on the SUPP10.							

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SUPPORT ROP Queries for Center 15-Stanford University

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per NG03 left eye reached ROP stage 3 in zone 2 but per SUPP10 highest stage in that zone was 2.							

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 final ROP status was 2='severe ROP' but that is not reflected on the SUPP10.								

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date(b) (6)								

Center ID number=15=Stanford University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated (b) (6) 8 highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.						

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SUPPORT ROP Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10.	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10.							

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 1. If this is correct, please F5 to confirm.								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye reached ROP stage 1 in zone 2 but per SUPP10 highest stage in that zone was 0.								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye reached ROP stage 1 in zone 3 but per SUPP10 highest stage in that zone was 0.								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had an exam with ROP stage 3 in zone 1 but that is not reflected on the SUPP10.	Per NG03 right eye had an exam with ROP stage 3 in zone 1 but that is not reflected on the SUPP10.							

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.	Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.							

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SUPPORT ROP Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date(b) (6)	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.						

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 stage 3 or worse ROP was diagnosed but that is not reflected on the SUPP10.								

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)								

Center ID number=16=University of Alabama Network number=81881 Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.								

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=16=University of Alabama Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 one or both eyes went from stage 2 or 3 ROP to mature within a week. If this is correct, please F5 to confirm.								

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.								

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SUPPORT ROP Queries for Center 16-University of Alabama

Center ID number=16=University of Alabama Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.							

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SUPPORT ROP Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 0.							

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 surgery was performed for ROP but that is not reflected on the SUPP10.								

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SUPPORT ROP Queries for Center 18-University of Texas-Houston

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.							

Center ID number=18=University of Texas-Houston Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=18=University of Texas-Houston Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=18=University of Texas-Houston Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10.	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10.							

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10.	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10.							

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 1 but per SUPP10 highest stage in that zone was 1.	Per NG03 right eye reached ROP stage 2 in zone 1 but per SUPP10 highest stage in that zone was 1.							

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.							

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.	Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.							

Center ID number=19=Duke University Network number (b) (6) **Date of Birth** (b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated 12/27/05 left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.								

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye had threshold ROP diagnosed but that is not reflected on the SUPP10.	Per NG03 right eye had threshold ROP diagnosed but that is not reflected on the SUPP10.							

Center ID number=19=Duke University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 infant had exam with mature vessels followed by an exam with stage 3 ROP in zone 1 (exams dated (b) (6) and (b) (6) .				

Query 8	Query resolution: Center notes

Center ID number=19=Duke University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=19=Duke University Network numbe(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.								

Center ID number=19=Duke University Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (b) (6)	Multiple ROP exams were entered on SUPP10 for the same date (b) (6) .	Multiple ROP exams were entered on SUPP10 for the same date (b) (6)						

Center ID number=19=Duke University Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=19=Duke University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=19=Duke University Network number(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) 9 left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

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SUPPORT ROP Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 20-Wake Forest University

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=20=Wake Forest University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 right eye reached ROP stage 2 in zone 2 but per SUPP10 highest stage in that zone was 1.								

Center ID number=20=Wake Forest University Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 left eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.	Per NG03 right eye reached ROP stage 3 in zone 1 but per SUPP10 highest stage in that zone was 0.							

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SUPPORT ROP Queries for Center 21-University of Rochester

Center ID number=21=University of Rochester Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated(b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated(b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

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SUPPORT ROP Queries for Center 22-University of California-San Diego

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (10/14/05).								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	Per SUPP10 highest stage ROP reached in left eye was stage 3 and highest in right eye was stage 1. If this is correct, please F5 to confirm.	Per SUPP10 surgery for ROP was performed in only one eye. If this is correct, please F5 to confirm.					

Query resolution: Center notes

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SUPPORT ROP Queries for Center 22-University of California-San Diego

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6) 6

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.								

Center ID number=22=University of California-San Diego Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had 2 exams with vessels in zone 3 followed by an exam with surgery for ROP. If this is correct, please F5 to confirm.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 22-University of California-San Diego

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	On SUPP10 exam dated (b) (6) right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.							

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=22=University of California-San Diego Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

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SUPPORT ROP Queries for Center 22-University of California-San Diego

Center ID number=22=University of California-San Diego Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=22=University of California-San Diego Network numbe(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date (02/13/09).								

Center ID number=22=University of California-San Diego Network numbe(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 surgery was performed for ROP but that is not reflected on the SUPP10.								

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SUPPORT ROP Queries for Center 23-Tufts University

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated 08/10/07 right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.								

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 ROP was diagnosed but ROP is not entered on SUPP10 exams.								

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.

Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.								

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.							

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SUPPORT ROP Queries for Center 23-Tufts University

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7
On SUPP10 exam dated (b) (6) left eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	On SUPP10 exam dated (b) (6) right eye had mature vessels but also has ROP. Per Dale Phelps this is not possible.	Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.				

Query 8	Query resolution: Center notes

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 infant had stage 4 or 5 ROP without a previous exam showing threshold ROP. If this is correct, please F5 to confirm.								

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.					

Query resolution: Center notes

Center ID number=23=Tufts University Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

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SUPPORT ROP Queries for Center 24-University of Iowa

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date(b) (6)								

Center ID number=24=University of Iowa Network number(b) (6) Date of Birth=.

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Multiple ROP exams were entered on SUPP10 for the same date(b) (6)								

Center ID number=24=University of Iowa Network number=(b) (6) Date of Birt(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per NG03 plus disease was diagnosed but that is not reflected on the SUPP10.								

Center ID number=24=University of Iowa Network number(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.	On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.						

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SUPPORT ROP Queries for Center 25-University of Utah

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.	On SUPP10 exam dated (b) (6) right eye meets criteria for Threshold ROP per MOP but Threshold not ='Y' on form.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	Per SUPP10 one or both eyes went from stage 2 or 3 ROP to mature within a week. If this is correct, please F5 to confirm.				

Query 8	Query resolution: Center notes

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SUPPORT ROP Queries for Center 25-University of Utah

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.	On SUPP10 exam dated (b) (6) left eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) right eye does not meet criteria for Threshold ROP per MOP but Threshold='Y' on form.								

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
Per SUPP10 left eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.	Per SUPP10 right eye had two exams with vessels in zone 3 but the last exam had stage 3 ROP. If this is correct, please F5 to confirm.							

Center ID number=25=University of Utah Network number=(b) (6) Date of Birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query 5	Query 6	Query 7	Query 8	Query resolution: Center notes
On SUPP10 exam dated (b) (6) highest ROP stage in lowest zone is > highest stage in any zone.								

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Missing_ROP

CENTER	NETWORK	ROP_message
5	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
5		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
9		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		The patient is within their Fol-up window and final ROP status has not been reported.
25		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates
Date: Friday, October 09, 2009 3:20:15 PM

The numbers are correct. Could more weight be given to the ranking based on enrollment numbers, and less weight given to the ranking based on percent enrolled?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 09, 2009 3:10 PM
To: Gantz, Marie; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Can you tell us if this looks ok?

I think the NRN PI's may have trouble with the order with respect to Rochester, Miami and Wake given the low numbers recruited in the study. Further, Wake was delayed getting IRB approval and Miami never went back to their IRB after the trial was restarted in 2006 as they knew they were no longer going to be in the network.

Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Friday, October 09, 2009 1:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Here's the order based on Marie's first two columns (number enrolled per SUPP02 and her calculation of those who met inclusion criteria).

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, October 06, 2009 5:19 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Numbers on infants enrolled and eligible by center are attached. Note that I calculated the numbers in two ways. First, I looked at infants who met the SUPPORT inclusion criteria (inborn, 24-27 weeks GA, to receive full resuscitation, and no known major congenital malformations). Second, I looked at those who were "eligible" by subtracting those who met exclusion criteria (born during a time when personnel and/or equipment were unavailable) from those who met inclusion criteria. (In 119 out of the 125 cases where exclusion criteria were met it was because personnel were not available.) The numbers are similar for most centers, but there is a difference for a few, most notably Brown. I will leave it to others to decide

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which set of numbers are more reasonable to use for authorship order.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, October 06, 2009 4:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Marie,

If you can send me the numbers by site, I'll plug them into my spreadsheet.

Thanks,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 06, 2009 2:07 PM
To: 'mgantz@rti.org'; 'adas@rti.org'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Can we use the SUPP02 numbers? This is more accrate
Rosemary D. Higgins, MD
Program Scientist

From: Gantz, Marie <mgantz@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>
Cc: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tue Oct 06 14:04:20 2009
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Rose,

The numbers in the spreadsheet appear to come from the latest monthly report where the number eligible is calculated as described in the footnote:

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Eligible GDB patients are those keyed in the NG02 (inborn and GA of 24 0/6 & 27 6/7) with a birth date after the first Support patient keyed for sites at each Center and not born on or between dates of Support study suspension 11/23/2005 and 2/5/2006.

As we have discussed before, these numbers do not match the numbers of infants on the SUPP02 which was supposed to be completed for "all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation" and which captures additional eligibility information. I would be inclined to use the SUPP02 numbers, but what do you think?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 11:41 AM
To: Gantz, Marie; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Marie/Abhik
Can you check our numbers to make sure we have the authorship order correct. Stephanie has put this together in order to move the papers along.

Thanks
Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, October 06, 2009 9:56 AM
To: 'Finer, Neil'; Wally Carlo (wcarlo@peds.uab.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Hi Neil and Wally,

Attached are two files, one for the Ventilation and one for the Oximetry papers, with the authors lists and boilerplates. The boilerplates are identical for both papers. The author lists have a few variations for the Yale and Cincinnati authors, as well as switching your names around. Author affiliations are included as footnotes. If you need me to copy these into your drafts, please send the drafts to me.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03

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From: Reubens, Linda
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Phelps, Dale; Jensen, Rosemary
Subject: RE: SUPPORT!!!
Date: Friday, October 09, 2009 8:48:45 AM

Hi Rose,
I recalled the medical record for Baby (b) (6) and have made the necessary corrections to the NGO7 form. We will make the corrections in the database next week and transmit.
Linda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 02, 2009 3:22 PM
To: Phelps, Dale; Reubens, Linda; Jensen, Rosemary
Cc: 'Gantz, Marie'
Subject: SUPPORT!!!
Importance: High

Hi,
Attached are BPD queries. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

Rosemary D. Higgins, MD
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From: Tinsley, Mazie L.
To: nell@rti.org; richard.ehrenkranz@yale.edu; roger.faix@hsc.utah.edu; ifrantz@tuftsmedicalcenter.org; goldb008@mc.duke.edu; Hale, Ellen; bpoindex@iupui.edu; Pablo.Sanchez@UTSouthwestern.edu; Shane, Andi L; sschrag@cdc.gov; Higgins, Rosemary (NIH/NICHD) [E]
Cc: barbara_stoll@oz.ped.emory.edu
Subject: FW: EOS paper
Date: Thursday, October 08, 2009 11:07:20 AM
Attachments: EOS Paper 10.08.09 NEJM.doc

To all authors of the EOS paper

Please review attached draft. We will add race-specific rates of infection (overall and for GBS and Ecoli) once we receive total livebirths by race from all centers (we have race data from most of you-- THANKS)

Look forward to your comments

Regards

BJS

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GBS and *E. Coli* Continue to Put Newborns at Risk for Early-Onset Sepsis: A Surveillance Study of ~300,000 live births

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Keywords: neonatal sepsis, Group B streptococcal disease, *Escherichia coli* infection

Word Count: 2,628

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ABSTRACT

Background: Guidelines for prevention of vertical transmission of Group B Streptococcal (GBS) disease have successfully reduced early-onset GBS disease. Several studies have suggested *Escherichia coli* is emerging as an early-onset sepsis (EOS) pathogen.

Objective: To determine current rates of EOS, associated pathogens, morbidity and mortality of infected newborns.

Design/Methods: Infants with EOS were identified by surveillance at centers of the NICHD Neonatal Research Network (NRN). EOS was defined by a positive blood culture obtained within 72 hours of birth plus antibiotic therapy for ≥5 days (or death <5 days/intent to treat). Maternal risk factors, intrapartum antibiotics, severity of neonatal illness, treatment and outcome were studied.

Results: Among 302,165 live births (2006-2008), 340 infants developed EOS (1.13 cases/1000 LB). Infection rates were inversely related to birth weight. GBS (37%) and *E. coli* (26%) were most frequently isolated. The majority of infants with GBS were term (71%); 81% with *E. coli* were preterm. Overall, 72% mothers had ≥1 risk factor for EO GBS, but only 53% received intrapartum antibiotics (66% preterm, 38% term). Placental pathology was performed for 63% cases, with histologic chorioamnionitis in 73%. While 74% infants required intensive care (96% early preterm, 78% late preterm, 53% term), 24% term infants were asymptomatic and treated in the term nursery. 15% infected infants died, most commonly preterm infants (24%) and those infected with *E. coli* (32%).

Conclusions: In the era of intrapartum antibiotic prophylaxis to prevent transmission of GBS, rates of EOS are low. GBS remains the most frequent pathogen for term infants and *E. coli* has emerged as the most significant pathogen for preterm infants. Missed opportunities for prevention of GBS remain. Prevention of *E. coli* sepsis, especially among preterm infants, remains a challenge.

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INTRODUCTION

Neonatal sepsis continues to be a serious problem among newborn infants. In the 1970's Group B streptococcal infections emerged as the leading cause of early-onset neonatal sepsis (EOS) and meningitis.[1] Prevention strategies to reduce vertical transmission of invasive GBS disease based on intrapartum chemoprophylaxis in at risk women (risk-based and screening-based) resulted in substantial reduction in early-onset (EO) GBS disease.[2,3] In an attempt to further reduce rates of EO GBS disease, the Centers for Disease Control and Prevention (CDC) recommended universal antenatal screening and intrapartum chemoprophylaxis for GBS positive women.[4] A further reduction in invasive GBS disease was reported following publication of these revised guidelines in 2002,[5] but missed opportunities for prevention remain.[6]

The epidemiology of neonatal sepsis is a changing landscape.[7,8] In the past decade, several studies have reported the emergence of *Escherichi coli* as an important cause of EOS, particularly among preterm infants.[9-14] Continued surveillance to monitor changes in pathogens associated with infection as well as changes in disease severity and outcome is important as we consider optimal prevention and treatment strategies. This study extends our earlier work on EOS among VLBW infants to all infants born at centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN)--a cohort of approximately 100,000 live births (LB) per year.

METHODS

Prospective surveillance for EOS and/or meningitis was conducted among LB infants of all gestational ages (GA) and with birthweight (BW) above 400 g who delivered at one of 16 NRN centers, February 1, 2006–December 31, 2008. EOS and meningitis were defined by isolation of a pathogen from blood (BC) or cerebrospinal fluid (CSF) cultures drawn within 72 hours of birth and antibiotic treatment for ≥5 days (or death <5 days/intent to treat). Cases were identified by research team review of patient, microbiology, or infection control/hospital epidemiology records.

Detailed maternal intrapartum and newborn information was collected including maternal screening for GBS and colonization status, intrapartum antibiotic (IAP) use within 72 hours prior to delivery, maternal risk factors for EO GBS, clinical and histologic chorioamnionitis. Risk factors for GBS sepsis included previous infant with GBS infection, maternal GBS bacteriuria, intrapartum fever (>100.4°F), delivery <37 weeks gestation, and ROM ≥ 18 hours prior to delivery. Neonatal information included infecting organism, antibiotic therapy initiated from birth through day of life 7, severity of illness, and outcome (death, discharge home, transfer). Antibiotic resistance data were collected on isolated pathogens if available from hospital microbiology records.

Statistical analysis

Cultures with growth of Micrococcus, Propionibacterium, or diphtheroids were considered contaminants. Cultures positive for coagulase-negative staphylococci (CoNS) were considered contaminants based on the attending physician's judgment and decision to discontinue antibiotics

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before day 5 in a surviving infant. Site variation in interpretation of CoNS cultures was examined. Infants with cultures positive for organisms considered to be contaminants were excluded from remaining analyses.

Maternal and neonatal characteristics of infants with early-onset infections were compared among early preterm (22-33 wks GA), late preterm (34-36 wks GA), and term (≥37 wks GA) infants. Maternal and infant antibiotic use was described, with emphasis on infants with *E. coli*, GBS, and CoNS. Infants were defined as symptomatic if they required intensive care or blood pressure support in the first 72 hours of life, or had respiratory distress, apnea, neutropenia (absolute neutrophil count<1000) or thrombocytopenia (platelet count<100,000).

Statistical significance for unadjusted comparisons of categorical variables was determined by chi-square tests and for adjusted comparisons using the Mantel-Haenszel method. EO infection rates were estimated as the number of infants diagnosed with EOS and/or meningitis divided by the total number of live births >400 grams BW during the study period. BW-specific rates were calculated using the number with EO infection and number of live births by BW group (401-1500 g, 1501-2500 g, >2500 g).

RESULTS

Between February 1, 2006 and December 31, 2008, 503 infants born at NRN hospitals had a positive blood and/or CSF culture in the first 72 hours of life. Among these, 163 infants were excluded from further analyses because the organism isolated was considered a contaminant; thus 340 infants were diagnosed with EOS and/or EOM. Coagulase-negative staphylococci were most frequently judged to be contaminants. Overall, 135 infants had a single early culture positive for CoNS (128 blood and 7 CSF cultures), of which 92 isolates (68%) were considered contaminants. Differences in interpretation of a single culture positive for CoNS exist across centers, although numbers at each center are small (Figure 1).

Early-onset sepsis rates

Among 302,165 infants born at NRN hospitals (2006-2008), 340 infants were diagnosed with EOS/EOM, for a rate of 1.13 cases per 1000 live births (range across study centers: 0.33-3.85 cases per 1000 infants, Figure 2). Infection rate was highest among infants 401-1500 g BW and lowest among those >2500 g (Table 1). Pathogens associated with infection changed with BW. Rates of infection with both *E. coli* and GBS were highest among VLBW infants and decreased with increasing BW. Rates of *E. coli* infection were higher than rates of GBS infection among VLBW infants (5.31 vs. 2.10) and LBW infants (0.49 vs. 0.38), while among infants >2500 g, GBS rates were higher than rates of *E. coli* (0.35 vs. 0.08).

Infant cultures and pathogens

While all infants had at least one BC performed (20% single BC, 48% 2 BCs, 32% >3 BCs), only 222 (65%) infants had a lumbar puncture (LP). Likelihood of an LP increased with increasing BW (401-1500g--48%; 1501-2500g--61%; ≥2501g--80%). Of note, 74% infants were being treated with antibiotics when the LP was performed, with a median time of 1 day between

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the blood and CSF cultures. Only 13/340 infants (4%) had a pathogen isolated from CSF; 6 of these infants had a negative BC (2% of all infants).

The most frequent EOS pathogen was GBS (37%) followed by *E. coli* (26%) and CoNS (13%, Table 2). No infections with methicillin resistant staphylococci or vancomycin resistant enterococci were identified. Eleven infants had polymicrobial infections (10 blood/one CSF). *E. coli* was the pathogen most frequently isolated from CSF (42%). All infants with *E. coli* in CSF also grew *E. coli* in blood. Among 146 early preterm infants (22-33 w), *E. coli* was the most frequent pathogen found in blood (43%) and in CSF (67%). Among 27 late preterm infants (34-36 w), 33% had GBS in blood, 26% had CoNS, and 19% had *E. coli*. GBS was the most frequent organism among term infants (57%). *E. coli* was the most frequent pathogen found in blood (46%) and CSF (67%) cultures for VLBW infants, 401-1500g BW, and the most frequent blood pathogen for LBW infants 1501-2500g BW (27%, no LBW infants had a postive CSF), while GBS was the most frequent pathogen found in blood for infants >2500 g BW (57%).

Antibiotic Resistance

78% of 79 *E. coli* isolates tested were resistant to ampicillin, 5% were resistant to gentamicin, and 4% were resistant to 3rd generation cephalosporins. Ampicillin resistance was more common among infants whose mothers received intrapartum ampicillin (87%) than among those whose mothers did not (68%, p=0.055). All 78 GBS isolates tested were sensitive to penicillin, ampicillin, and vancomycin. Of 36 GBS isolates tested, 22% were resistant to clindamycin. All 43 CoNS isolates tested were sensitive to vancomycin, but 54% were resistant to oxacillin and 21% were resistant to gentamicin.

Infant antibiotic therapy

Ampicillin and gentamicin were the antibiotics most frequently started for presumed early infection (Table 3); 21% infants were treated with cefotaxime, with highest use among infants with *E. coli* (49%) and other gram negative infections (44%). 18% were treated with vancomycin, with highest use among infants with CoNS (47%) and other gram positive infections (26%). Infants with *E. coli* and CoNS infections were more likely to have a change in initial empiric antibiotic therapy, with exposure to 3 or more drugs for treatment of their early-onset infections (*E. coli*=75%; CoNS=58%; GBS=29%).

Maternal and infant characteristics and risk factors for GBS and E.coli EOS

Over half of mothers of infants with early infections (53%) received intrapartum antibiotics, with the proportion highest among mothers of early preterm infants (Table 4). Overall, 62% mothers were screened for GBS. Despite current CDC recommendations for universal screening, only 67% mothers who delivered at term had been screened for GBS; screening was less common for women delivering preterm (58%). Among those screened, 27% were colonized with GBS, with no difference in colonization rates by GA. Among term infants, the percent of mothers treated with IAP was higher in those who screened positive for GBS, but overall only 73% of those with GBS colonization received IAP. The proportion of mothers who received antibiotics increased with increasing duration between admission and delivery: <4 hours, 38%; 4-24 hours, 48%; >24

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hours, 66%; p<0.001. Prophylaxis for GBS, suspected chorioamnionitis, and fever were the most common reasons for administration of antibiotics intrapartum. Ampicillin (36%), gentamicin (19%), erythromycin (11%), and penicillin (9%) were the most commonly administered antibiotics, Table 5.

The majority of infants with GBS were term (71%), while the majority of infants with *E. coli* were preterm (81%) (Table 6). Infants infected with GBS were more likely than infants with *E. coli* to be Black (51% vs 30%). Overall, only 55% of mothers whose infants developed EO GBS were screened for GBS (59% term, 46% preterm) and of those who were colonized, only 55% received IAP. In our cohort of infected infants, 78% of term and 25% of preterm infants with EO GBS had a negative maternal GBS colonization screen.

Among preterm infants, the proportion of mothers who had an elevated temperature, uterine or abdominal tenderness, and foul smelling vaginal discharge or amniotic fluid in the 72 hours prior to delivery was higher for mothers of infants infected with *E. coli* than for mothers of infants with GBS infections, although differences were statistically significant for maternal temperature only. Chorioamnionitis was more frequently documented in the medical record for mothers of infants with *E. coli* than with GBS (55% vs. 36% overall, adjusted p=0.054). After adjusting for GA group, no differences were found in the proportion of infants with GBS and *E. coli* whose mothers had placental pathology performed or histologic chorioamnionitis documented. Among women with chorioamnionitis recorded in the medical record, 77% had placental pathology performed. Of these, histologic chorioamnionitis was documented for 90%.
Mothers of early preterm infants were more likely to have placental pathology (84%) compared to mothers of late preterm (58%) or term (44%) infants. Histologic chorioamnionits was documented more frequently for mothers of early preterm infants (80%) than for mothers of late preterm (60%) or term (64%) infants.

Clinical Care and Outcome

Given that more infants with *E. coli* were preterm, it was expected that a higher proportion of infants with *E. coli* received intensive care (90%) compared to those with GBS (64%) or CoNS (67%) (Table 7). Among infants who received intensive/intermediate care, a greater proportion of those with *E. coli* infections had respiratory distress and apnea compared to infants with either GBS or CoNS; however, among preterm infants the proportion with respiratory distress was similar for infants with *E. coli* (95%) and GBS infections (94%) while for infants with CoNS the proportion was lower (76%). Blood pressure support was most likely to be given to infants with *E. coli* and least likely for infants with CoNS. A lower proportion of infants with CoNS had neutropenia (11%) than did infants with GBS (25%) or *E. coli* EOS (34%). Thrombocytopenia was most common among infants with *E. coli.*

While the vast majority of infants with EOS/EOM survived to discharge, 15% died. Mortality and timing of death varied by GA and BW, p<0.001 (Table 8). The proportion of infants who died <3 days of life was highest for infants born at the lowest GA and BW. More infants with *E. coli* EOS died (32%) compared to infants with GBS (11%) and CoNS (5%). However, among preterm infants, the proportion of infants with *E. coli* infection who died was closer to the proportion with GBS who died (37% vs. 31%).

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DISCUSSION

The epidemiology of EOS is a changing landscape. Studies over time have demonstrated changes in the predominant organisms associated with infection.[7-9] National guidelines to prevent vertical transmission of GBS disease based on intrapartum antibiotic prophylaxis in at risk women (GBS screen positive or risk factors for GBS in non-screened women) have been a great success.[5,6,15] Our study confirms that in the era of intrapartum chemoprophylaxis, overall rates of EOS are low (1.13/1000 live births). GBS remains the most frequent EOS pathogen, especially for term infants. Missed opportunities for prevention of GBS continue, including failure to screen all women who deliver at term, unknown colonization status of many women who deliver preterm infants, false negative GBS screens among some women who deliver infants with GBS infection, and failure to treat all women who are known to be colonized with GBS. Creative strategies will be needed to increase adherence to prevention guidelines and further reduce EO GBS cases among term and preterm infants.

Several studies have documented increased rates of *E. coli* infection among preterm infants in recent years [8,9] This prospective surveillance study of over 300,000 live births confirms that *E. coli* has emerged as the most frequent EOS pathogen among preterm infants and that infants with *E. coli* infections are at highest risk of severe disease and death. Prevention strategies for early-onset *E. coli* disease need to be developed and tested. Similar to what has been done with GBS, analysis of risk factors associated with EO *E. coli* will be useful to identify high risk women to target for prevention.

Bacteremia is a known risk factor for neonatal meningitis.[16] In our cohort, only two thirds of infants with EOS had an LP performed. More term infants underwent an LP, in large part because VLBW preterm infants are often considered too unstable to tolerate an LP. Although most CSF cultures were negative, 74% infants had their LP performed after initiation of antibiotics, potentially sterilizing an infected CSF and making a diagnosis of meningitis more difficult. Although the number of infants with a positive CSF culture in the face of a negative blood culture was low, these cases are a reminder that meningitis will be missed in some infants if an LP is not part of the sepsis work-up.

The importance of CoNS as EOS pathogens remains unclear. In our cohort, over half of early blood cultures positive for CoNS were judged to be contaminants, with wide center variability in assessment of a single BC positive for CoNS. Although mortality was low among infants judged to have a "real" CoNS infection, 67% were treated in the intensive care unit. Prospective studies of the vaginal ecology of pregnant women, vertical transmission of CoNS, as well as continued surveillance for these organisms among newborn infants with EOS will help determine if CoNS are emerging as important EOS pathogens.

Rational choice of antibiotics requires review of antibiotic susceptibility of the predominant organisms causing disease at the local level.[17] Ampicillin and gentamicin continue to be the recommended empiric antibiotics for the infant at risk for EOS.[18] Our study supports this recommendation as all GBS isolates were sensitive to ampicillin and 95% of *E. coli* isolates were sensitive to gentamicin. That said, treatment of the specific infant must be guided by antibiotic susceptibility of the infecting organism and clinical course.

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With current neonatal intensive care, the vast majority of infants with EOS survive. The most immature infants and those infected with *E. coli* remain at highest risk of death. Although improved treatment strategies may reduce the current 15% mortality, strategies to reduce the unacceptably high rates of preterm birth in the United States are more likely to reduce deaths associated with early-onset infections, as well as deaths related to other complications of prematurity.

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Figure 1.

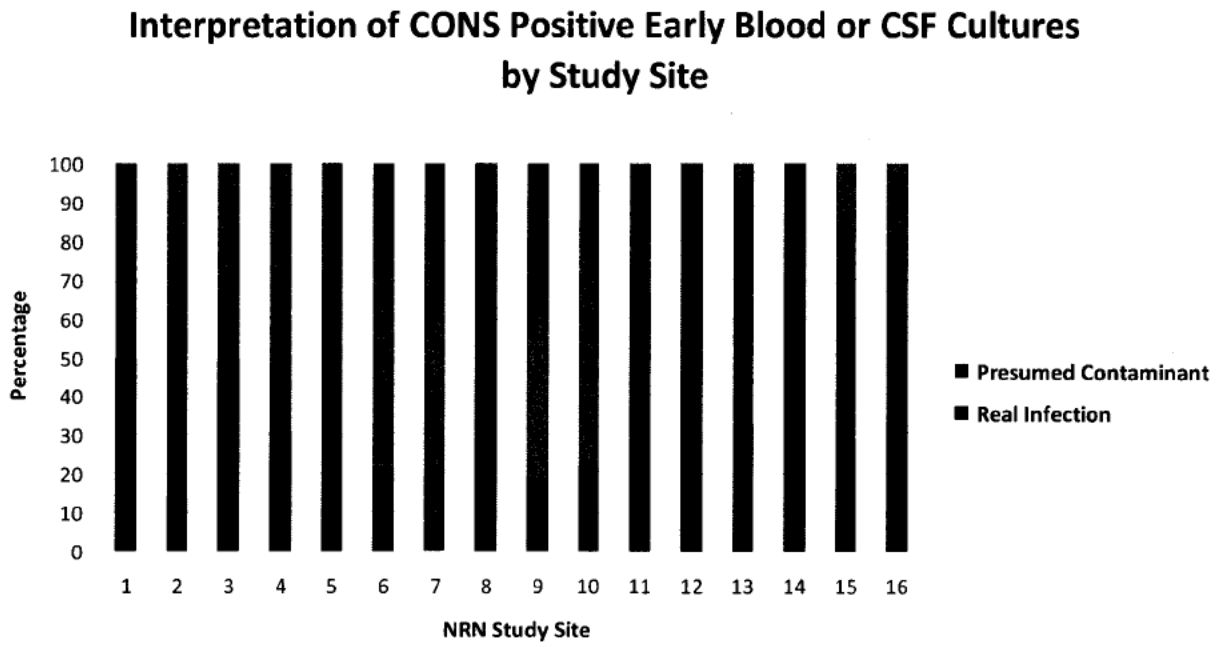

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Figure 2.

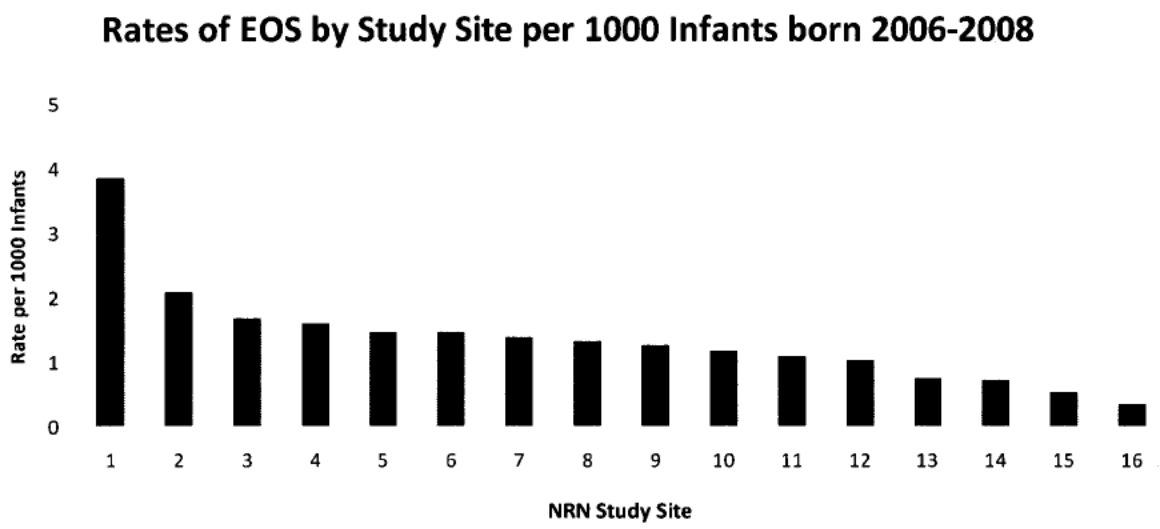

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Table 1. Rates of early-onset infections (All, GBS, *E. coli*) per 1000 live births at NICHD Neonatal Research Network study hospitals, February 2006-December 2008.

	Rates by Birthweight			
Pathogen	**401-1500 grams**	**1501-2500 Grams**	**>2500 grams**	**All BW**
All	12.32	1.78	0.63	1.13
GBS	2.10	0.38	0.35	0.41
E. coli	5.31	0.49	0.08	0.29

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Table 2. Pathogens associated with early-onset sepsis and meningitis, NICHD Neonatal Research Network, February 2006-December 2008 [1/]

Pathogen	Sepsis N	Sepsis %	Meningitis* N	Meningitis* %
Gram-positive	**214**	**66**	**6**	**50**
Group B streptococcus	121	37	2	17
Coagulase-negative staphylococcus	43	13	-	-
Viridans streptococcus	11	3	2	17
Staphylococcus aureus	9	3	1	8
Enterococcus	8	2	1	8
Group A streptococcus	6	2	-	-
Other gram-positive[2/]	16	5	-	-
Gram-negative	**108**	**33**	**6**	**50**
E. coli	84	26	5	42
Haemophilus sp.	10	3	-	-
Other gram-negative[3/]	14	4	-	-
Total	**322**	**100**	**12**	**100**

[1/] Ten infants with the following polymicrobial infections were excluded from the table: GBS + *E. coli* (3), enterococcus + CoNS (2), Neisseria + Hemophilus (1), Neisseria + Streptococcus viridans (1), klebsiella + Candida albicans (1), Pseudomonas aeruginosa + Enterobacter (1), group A Streptococcus + CoNS (1).

[2/] Alpha streptococcus (1), Streptococcus pneumoniae (2), Streptococcus bovis/gallolyticus (3), bacillus (3), Listeria monocytogenes (2), Actinomyces odontolyticus (1), Gram positive rods, CDC Group A (1), Gram positive cocci in chains and pairs (1), non-spore forming Gram positive rod (1), aerobic Gram positive bacilli, not lysteria/erysipelothrix/bacillus (1).

[3/] Enterobacter (3), Citrobacter (2), Acinetobacter (1), Klebsiella (1), Pseudomonas aeruginosa (1), Bacteroides (3), Moraxella (1), Morganella morganii (1), Capnocytophaga sp. (1).

*For seven infants, the same organism was found on CSF and blood cultures (5 *E. coli*, 1 viridans streptococcus, 1 GBS). Six infants had positive CSF cultures, but negative CSF cultures. One of these infants had a polymicrobial culture on CSF that was considered a true infection by the attending physician. This infant was included as a case of EOM, but organisms were not listed on the table.

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Table 3. Infant antibiotic therapy started in the first 7 days of life—percent of infants who received each drug, overall and by infecting pathogens, NICHD Neonatal Research Network, February 2006-December 2008*

Drug, n (%)	GBS N=122	*E. coli* N=84	CoNS N=43	All infants N=340
Ampicillin	121 (99)	83 (99)	43 (100)	335 (99)
Other penicillins [1/]	19 (16)	7 (8)	3 (7)	37 (11)
Gentamicin	120 (98)	80 (95)	41 (95)	330 (97)
Other aminoglycosides [2/]	0 (0)	1 (1)	0 (0)	2 (<1)
Vancomycin	11 (9)	9 (11)	20 (47)	61 (18)
Cefotaxime	7 (6)	41 (49)	3 (7)	72 (21)
Other cephalosporins [3/]	1 (<1)	13 (15)	4 (9)	22 (6)
Other antibiotic [4/]	3 (2)	22 (26)	1 (2)	31 (9)

*All except two of the 340 infants with EO infections were treated with antibiotics. Antibiotics were ordered but not given to one infant (GA 25 w) with GBS who died 6 hours after birth. The other infant (GA 40 w) had profound hypoxia-ischemia after a difficult resuscitation and the clinical care team did not entertain the possibility that there may have been sepsis as a predisposing factor. This infant had *E. coli* EOS and died 8 hours after birth.

[1/] Includes nafcillin, oxacillin, penicillin G, piperacillin.

[2/] Includes amikacin, tobramycin.

[3/] Includes cefazolin, cefepime, ceftazidime, ceftriaxone, cefuroxime.

[4/] Includes azithromycin, clindamycin, erythromycin, imipenem, meropenem, metronidazole, piperacillin + tazobactam (zosyn)

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Table 4. Maternal characteristics and risk factors for sepsis among infants with early-onset sepsis and/or meningitis, NICHD Neonatal Research Network, February 2006-December 2008

Characteristic, n (%) [1/]	**Early Preterm** (22-33 w) N=153	**Late Preterm** (34-36 w) N=27	**Term** (37+ w) N=160	**Overall** N=340
Mother's age, mean (STD)**	27 (6.6)	26 (6.0)	25 (6.4)	26 (6.5)
Prenatal visit **	148 (98)	24 (89)	159 (99)	331 (98)
Antibiotics w/in 72 h prior to delivery ***	102 (67)	17 (63)	61 (38)	180 (53)
Antenatal steroids w/in 72 h prior to delivery ***	89 (58)	3 (11)	0 (0)	92 (27)
Type of delivery [2/]				
Vaginal vertex	52 (34)	12 (44)	80 (50)	144 (43)
Vaginal breech	8 (5)	0 (0)	0 (0)	8 (2)
Vaginal NOS	4 (3)	0 (0)	4 (3)	8 (2)
C-section w/labor	49 (32)	7 (26)	58 (36)	114 (34)
C-section w/out labor	27 (18)	6 (22)	6 (4)	39 (12)
C-section NOS	12 (8)	2 (7)	11 (7)	25 (7)
Screened for GBS**				
Yes	88 (58)	16 (59)	107 (67)	211 (62)
No	34 (22)	10 (37)	42 (26)	86 (25)
Unknown	31 (20)	1 (4)	11 (7)	43 (13)
GBS screen result [3/]				
Positive	28 (32)	5 (31)	23 (21)	56 (27)
Negative	60 (68)	10 (63)	83 (78)	153 (73)
Unknown	0 (0)	1 (6)	1 (<1)	2 (<1)
Risk factor for early-onset GBS at time of delivery [4/] ***	147 (96)	24 (89)	68 (44)	239 (72)
Spontaneous rupture of membranes w/ or w/out labor before 37 w ***	120 (78)	14 (52)	1 (<1)	135 (40)
Maternal temperature $\geq$ 100.4°F **	25 (17)	5 (19)	51 (32)	81 (24)
Uterine or abdominal tenderness ***	36 (24)	1 (4)	7 (4)	44 (13)
Foul smelling vaginal discharge or amniotic fluid ***	22 (14)	0 (0)	5 (3)	27 (8)
Maternal tachycardia (>100 beats per min)	49 (32)	8 (31)	36 (23)	93 (28)
Fetal tachycardia (>160 beats per min)	45 (30)	3 (12)	47 (30)	95 (28)

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Table 4. (continued)

Characteristic, n (%)	**Early Preterm** (22-33 w) N=153	**Late Preterm** (34-36 w) N=27	**Term** (37+ w) N=160	**Overall** N=340
Chorioamnionitis documented in the medical record*	69 (45)	6 (23)	56 (35)	131 (39)
Placental pathology performed***	127 (84)	15 (58)	70 (44)	212 (63)
Histologic chorioamnionitis[5/]*	101 (80)	9 (60)	45 (64)	155 (73)

[1/] Information was missing for prenatal visit: 2 infants; maternal antibiotics: 1; delivery type: 2; risk factor for early-onset GBS: 6; spontaneous rupture of membranes < 37 weeks: 1; maternal temperature, uterine or abdominal tenderness, foul smelling vaginal discharge/ amniotic fluid, maternal tachycardia, fetal tachycardia: 3; chorioamnionitis in the medical record: 3; placental pathology: 5.

[2/] No significant difference between gestational age groups in the proportion with c-section vs. vaginal delivery.

[3/] From among mothers screened for GBS.

[4/] One or more of: previous infant with GBS, GBS bacteriuria, intrapartum fever, delivery < 37 weeks gestation, ROM ≥ 18 hours prior to delivery.

[5/] From among mothers who had placental pathology performed.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ for a difference between gestational age groups by the chi-square test or the Kruskal-Wallis test (mother's age).

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Table 5. Maternal antibiotic therapy during the delivery admission within 72 hours prior to delivery, percent of infants whose mothers received each drug, overall and by infecting pathogens, NICHD Neonatal Research Network, February 2006-December 2008

Drug, n (%)	GBS N=122	*E. coli* N=83*	CoNS N=42*	All infants N=338*
Ampicillin	35 (29)	49 (59)	9 (21)	122 (36)
Oxacillin	0 (0)	1 (1)	0 (0)	1 (<1)
Penicillin G	8 (7)	9 (11)	5 (12)	30 (9)
Amoxicillin	0 (0)	4 (5)	0 (0)	7 (2)
Cefazolin	3 (2)	7 (8)	4 (10)	20 (6)
Ceftriaxone	1 (<1)	1 (1)	0 (0)	3 (<1)
Gentamicin	23 (19)	22 (27)	3 (7)	63 (19)
Clindamycin	3 (2)	6 (7)	3 (7)	16 (5)
Erythromycin	3 (2)	22 (27)	1 (2)	37 (11)
Azithromycin	2 (2)	3 (4)	1 (2)	7 (2)
Metronidazole	0 (0)	3 (4)	0 (0)	3 (<1)
Other antibiotic	2 (2)	13 (16)	2 (5)	24 (7)

* Maternal antibiotic therapy information is missing for mothers of 2 infants: no information was available as to whether or not the mother of an infant with E coli received antibiotics; the mother of an infant with CoNS received antibiotics but no information was available about which drugs were received.

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Table 6. Infant and maternal characteristics and risk factors for infants with GBS and *E. coli* early-onset sepsis, NICHD Neonatal Research Network, February 2006-December 2008[1/]

Characteristic, n (%) [2/]	**Preterm (22-36 w)**		**Term (37+ w)**		**Overall**		
	GBS N=35	***E. coli*** **N=68**	**GBS N=87**	***E. coli*** **N=16**	**GBS N=122**	***E. coli*** **N=84**	**Unadjusted (Adjusted) p-value** [3/]
Infant characteristics							
Birth weight (grams)							<0.001 (0.06)
401-1500	21 (60)	53 (78)	0	0	21 (17)	53 (63)	
1501-2500	10 (29)	14 (21)	1 (1)	0 (0)	11 (9)	14 (17)	
2501+	4 (11)	1 (1)	86 (99)	16 (100)	90 (74)	17 (20)	
Sex							0.3 (0.2)
M	20 (57)	38 (56)	45 (52)	13 (81)	65 (53)	51 (61)	
F	15 (43)	30 (44)	42 (48)	3 (19)	57 (47)	33 (39)	
Race/ ethnicity							0.001 (0.01)
Black, non-Hispanic	19 (54)	20 (29)	43 (49)	5 (31)	62 (51)	25 (30)	
White, non-Hispanic	6 (17)	26 (38)	17 (20)	6 (38)	23 (19)	32 (38)	
Hispanic	8 (23)	16 (24)	26 (30)	4 (25)	34 (28)	20 (24)	
Other	2 (6)	6 (9)	1 (1)	1 (6)	3 (2)	7 (8)	
Maternal characteristics							
Mother's age, mean (STD)	25 (6.1)	28 (6.2)	23 (5.6)	30 (6.7)	23 (5.7)	29 (6.3)	<0.001 (<0.001)
Type of delivery							0.05 (0.9)
Vaginal vertex	12 (34)	19 (28)	44 (51)	6 (40)	56 (46)	25 (30)	
Vaginal breech	2 (6)	3 (4)	1 (1)	1 (7)	2 (2)	3 (4)	
Vaginal NOS	1 (3)	0 (0)	34 (39)	6 (40)	2 (2)	1 (1)	
C-section w/labor	12 (34)	25 (37)	2 (2)	1 (7)	46 (38)	31 (38)	
C-section w/out labor	5 (14)	14 (21)	6 (7)	1 (7)	7 (6)	15 (18)	
C-section NOS	3 (9)	6 (9)	44 (51)	6 (40)	9 (7)	7 (9)	

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Table 6. (continued)

Characteristic, n (%) [2/]	Preterm (22-36 w)		Term (37+ w)		Overall		
	GBS N=35	*E. coli* N=68	GBS N=87	*E. coli* N=16	GBS N=122	*E. coli* N=84	Unadjusted (Adjusted) p-value [3/]
Screened for GBS							0.03 (0.04)
Yes	16 (46)	43 (63)	51 (59)	13 (81)	67 (55)	56 (67)	
No	13 (37)	12 (18)	29 (33)	3 (19)	42 (34)	15 (18)	
Unknown	6 (17)	13 (19)	7 (8)	0 (0)	13 (11)	13 (15)	
GBS screen result [4/]							0.3 (0.02)
Positive	12 (75)	9 (21)	10 (20)	4 (31)	22 (33)	13 (23)	
Negative	4 (25)	33 (77)	40 (78)	9 (69)	44 (66)	42 (75)	
Unknown	0 (0)	1 (2)	1 (2)	0 (0)	1 (1)	1 (2)	
Risk factor for early-onset GBS at time of delivery [5/]	35 (100)	65 (96)	37 (44)	6 (40)	72 (60)	71 (86)	<0.001 (0.5)
Spontaneous rupture of membranes w/ or w/out labor before 37 w	24 (69)	57 (84)	NA	NA	NA	NA	0.08[6/]
Maternal temperature ≥ 100.4°F	3 (9)	18 (27)	31 (36)	4 (25)	34 (28)	22 (27)	0.9 (0.3)
Uterine or abdominal tenderness	6 (17)	18 (27)	4 (5)	0 (0)	10 (8)	18 (22)	0.007 (0.4)
Foul smelling vaginal discharge or amniotic fluid	2 (6)	11 (17)	1 (1)	0 (0)	3 (2)	11 (13)	0.004 (0.2)
Maternal tachycardia (>100 beats per min)	13 (37)	25 (38)	19 (22)	6 (38)	32 (26)	31 (38)	0.09 (0.4)
Fetal tachycardia (>160 beats per min)	9 (26)	26 (39)	29 (33)	6 (38)	38 (31)	32 (39)	0.3 (0.2)
Chorioamnionitis documented in the medical record	12 (34)	39 (59)	32 (37)	6 (38)	44 (36)	45 (55)	0.01 (0.05)
Placental pathology performed	28 (80)	57 (86)	39 (45)	10 (63)	67 (55)	67 (82)	<0.001 (0.1)
Histologic chorioamnionitis[7/]	26 (93)	52 (91)	26 (67)	6 (60)	52 (78)	58 (87)	0.3 (0.6)

[1/] Three infants with both GBS and *E. coli* were excluded from this table.

[2/] Information was missing for delivery type: 2 infants; maternal risk factor for GBS: 3; maternal temperature, uterine or abdominal tenderness, foul smelling vaginal discharge/amniotic fluid, maternal tachycardia, fetal tachycardia: 2; chorioamnionitis in the medical record: 2; placental pathology: 3.

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[3/] P-value for a difference between infants with GBS versus *E. coli* overall unadjusted and adjusting for GA group (preterm, term).

[4/] From among mothers screened for GBS.

[5/] One or more of: previous infant with GBS, GBS bacteriuria, intrapartum fever, delivery < 37 weeks gestation, ROM ≥ 18 hours prior to delivery.

[6/] P-value for a difference between infants with GBS versus *E. coli* among preterm infants.

[7/] From among mothers who had placental pathology performed.

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Table 7. Clinical care and outcomes for infants with early-onset infections (All pathogens, GBS, *E. coli*, and CoNS), NICHD Neonatal Research Network, February 2006-December 2008

Characteristic, n (%)[1/]	**GBS N=122**	***E. coli* N=84**	**CoNS N=43**	**Overall** N=340
Highest care area***				
Well baby nursery	26 (21)	4 (5)	5 (12)	42 (12)
Intermediate care/step down/transitional	18 (15)	4 (5)	9 (21)	46 (14)
Intensive care	78 (64)	76 (90)	29 (67)	252 (74)
Infants who received intensive or intermediate care	N=96	N=80	N=38	N=298
Respiratory distress*	84 (88)	74 (93)	28 (74)	253 (85)
Apnea**	26 (27)	40 (50)	10 (26)	100 (34)
BP support				
Volume expansion***	30 (31)	48 (60)	10 (26)	116 (39)
Pressor***	25 (26)	38 (48)	5 (13)	82 (28)
Steroids***	8 (8)	21 (26)	2 (5)	33 (11)
Neutropenia [2/] *	23 (25)	26 (34)	4 (11)	65 (23)
Thrombocytopenia [3/] ***	13 (14)	34 (43)	2 (5)	60 (20)
All infants				
Symptomatic [4/] **	94 (77)	80 (95)	35 (81)	284 (84)
Symptomatic (excluding intensive care) [4/] ***	87 (71)	77 (92)	30 (70)	264 (78)

[1/] Three infants with both GBS and *E. coli* and 3 infants with polymicrobial infections that included CoNS were excluded from this table.
Highest care area and symptomatic percents are among all 249 infants with GBS, *E. coli*, and CoNS infections included in the table. Respiratory distress, apnea, blood pressure support, neutropenia, and thrombocytopenia were reported only for the 214 infants who received intensive and intermediate care.

[2/] Defined as absolute neutrophil count<1000 based on the lowest count in the first 72 hours. Information was missing for 11 infants who received intensive or intermediate care.

[3/] Defined as platelet count<100,000 based on the lowest count in the first 72 hours. Information was missing for 1 infant who received intensive or intermediate care.

[4/] Infants were defined as symptomatic if they required intensive care or blood pressure support in the first 72 hours of life, or had respiratory distress, apnea, neutropenia or thrombocytopenia. Alternatively, requiring intensive care was excluded from the definition.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ for a difference between pathogen groups by the chi-square test.

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Table 8. Mortality and timing of death by gestational age, birth weight, and infecting pathogen, NICHD Neonatal Research Network, February 2006-December 2008

	Deaths	Timing of Deaths			
	N %	0-3 days	>3-7 days	>7-14 days	>14 days
Overall, N=340	50 (15%)	28 (8%)	9 (3%)	2 (<1%)	11 (3%)
Gestational age, weeks					
22-24, n=42	22 (52%)	13 (31%)	2 (5%)	2 (5%)	5 (12%)
25-28, n=62	15 (24%)	9 (15%)	3 (5%)	0	3 (5%)
29-33, n=49	6 (12%)	2 (4%)	2 (4%)	0	2 (4%)
34-36, n=27	1 (4%)	1 (4%)	0	0	0
37+, n=160	6 (4%)	3 (2%)	2 (1%)	0	1 (<1%)
Birth weight, grams					
401-500, n=4	2 (50%)	1 (25%)	0	0	1 (25%)
501-750, n=42	20 (48%)	11 (26%)	2 (5%)	1 (2%)	6 (14%)
751-1000, n=34	11 (32%)	7 (21%)	2 (6%)	1 (3%)	1 (3%)
1001-1250, n=25	4 (16%)	3 (12%)	1 (4%)	0	0
1251-1500, n=18	3 (17%)	1 (6%)	0	0	2 (11%)
1501-2500, n=51	4 (8%)	2 (4%)	2 (4%)	0	0
2501+, n=166	6 (4%)	3 (2%)	2 (1%)	0	1 (<1%)
Infecting Pathogen					
GBS, n=122	13 (11%)	7 (6%)	1 (<1%)	0	5 (4%)
E. coli, n=84	27 (32%)	18 (21%)	5 (6%)	1 (1%)	3 (4%)
CoNS, n=43	2 (5%)	1 (2%)	1 (2%)	0	0
Other pathogen, n=80	6 (8%)	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Polymicrobial, n=11	2 (18%)	1 (9%)	0	0	1 (9%)

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Thursday, October 08, 2009 11:06:28 AM

How about the 23rd to give time for processing, Marie to run the reports and the reviewers to review the cases prior to the call?
thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 10/8/2009 11:03 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: Re: SUPPORT

Could we do late in that week?
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik <adas@rti.org>
Sent: Thu Oct 08 10:16:34 2009
Subject: RE: SUPPORT

Hi Rose,

Marie pointed out that is might be better to wait until after the 20th because that is the deadline we gave the sites to get data in and we would then need to process any transmissions the night of the 20th to get completely up to date data. Please let me know what you think.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 10/8/2009 9:00 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: Re: SUPPORT

Just use reports from the dms.
Rosemary D. Higgins, MD

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Program Scientist

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik <adas@rti.org>
Sent: Thu Oct 08 08:46:06 2009
Subject: RE: SUPPORT

Hi,

The data was updated last night and processing today; will check with Marie and Dr. Wallace about the date. Do we need the actual reports or in some cases pictures from the all sites to review; if so, it will likely take a week or two to request these, make copies and get them to the folks that are reviewing them, or, are we just talking about the Duke cases?

Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 10/8/2009 6:46 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: SUPPORT

Kris
Are you and marie available on the afternoon of october 20 for a SUPPORT ROP call with Dale? If so, can you ask Dr. Wallace from Duke if he can join and we can decide about the cases with unknown outcome. If that day doesn't work, we can try later in the week.

Also, do you have the updated list of the 64 duke patients for them to certify the outcomes?

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: case question
Date: Wednesday, October 07, 2009 12:35:00 PM

How are these being handled??

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, October 07, 2009 12:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Phelps, Dale; David K Wallace; Ronald N Goldberg; Kimberley A Fisher; Zaterka-Baxter, Kristin
Subject: RE: case question

ok....just so i'm straight then...if the after 55 weeks exam is the final outcome..should the answer to the question about final status at 55 weeks be 'yes' lost...and the answer to the question about final status determined at 18 months also be 'yes'?

(sorry to bug you about this...but I want to make sure that what we plug in is correct)

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>	To	"'Michael Cotten'" <cotte010@mc.duke.edu>
10/07/2009 10:54 AM	cc	"Phelps, Dale" <Dale_Phelps@URMC.Rochester.edu>, Ronald N Goldberg <goldb008@mc.duke.edu>, Kimberley A Fisher <kimberley.fisher@duke.edu>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, David K Wallace <david.wallace@duke.edu>
	Subject	RE: case question

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If the exam was done after discharge, the GDB outcome is undetermined. However, for SUPPORT, we can use the exam after 55 weeks for final outcome (we know that some of them become final as late as 7-8 months). Enter the date of the exam and the exam results as fully mature and this should suffice as a 'determined" SUPPORT outcome.

Thanks
Rose

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, October 07, 2009 10:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Phelps, Dale; Ronald N Goldberg; Kimberley A Fisher; Zaterka-Baxter, Kristin; David K Wallace
Subject: RE: case question

Hi again Rose and team (including David Wallace this time)...another tough one to call (the last one re-reviewed actually of the 64 at Duke..)...case number 72421, another one with exam at 45 weeks pma, the 8th exam in a row of stage 2, zone 2 bilaterally.....again exam by David,,,,,next exam is scheduled for '1 year later' but is seen 4 months later (after 55 weeks), w/ stage 0, zone 4 fully vascularized....

would this one be a 'yes' to final status lost to followup at 55 weeks? I think it would be a yes....but again, David W's take on what's a favorable outcome (or definite enough at 45 weeks to allow a big window til next exam that then occurs after 55 weeks) is different from the listed outcomes in the MOP...

for reference here's David's response on the similar case:

"There are 4 reasons to stop screening, and this child had #3 and #4.

Here is the excerpt from the AAP/AAO screening guidelines paper:

(Embedded image moved to file: pic60036.gif)
I don't suggest changing an outcome, but there could be a clarification that any of these 4 meet criteria for "favorable status."

and the MOP:

15.2 Acute/final Status
An eye is 'acute/final" when it reaches one of the following points in time:
These can be a good outcome (favorable) as the ROP heals (regresses), or it can be the

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primary outcome variable event (unfavorable).
Favorable
* Vessel growth if mature to the ora serrata in all clock hours
* Vessels in zone III for two sequential eye examinations
(i.e. two examinations in a row)
Unfavorable
* type I threshold ROP
* Laser (or cryo or both) surgery for acute ROP
* retinal detachment stage 5 retinal detachment stage 4b
Other
* Infant dies.

so it's confusing..because if ophthalmologists then scheduled visits well beyond 55 weeks and its w/in their standard of care to do so....not sure if a site (ours and maybe others???) can be at fault w/ a 'missing outcome' if the baby wasn't back in that 10 week window between 45 and 55 weeks....

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Q for the SUPPORT call
Date: Wednesday, October 07, 2009 10:40:00 AM

YES
Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 07, 2009 10:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Q for the SUPPORT call

Hi Rose,

Are you planning to bring up the question of how kids on room air by CPAP or vent should be classified for the "traditional" BPD outcome?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From:	Huitema, Carolyn Petrie
To:	Huitema, Carolyn Petrie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Wally Carlo, M.D.; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc:	Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject:	RE: NRN Calls-SUPPORT Call
Date:	Wednesday, October 07, 2009 10:14:24 AM
Attachments:	FINAL_Grid_SUPPORTSchoolAge_visit.pdf

Due to some technical error, the grid for Dr. Hintz's study saved as the protocol.
Attached is the correct file.

From: Huitema, Carolyn Petrie
Sent: Wednesday, October 07, 2009 9:26 AM
To: 'Finer, Neil'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Poole, W. Kenneth; Wallace, Dennis; 'Wally Carlo, M.D.'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger.Faix@hsc.utah.edu'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'kurt.schibler@cchmc.org'; 'nancy newman'; 'Rich, Wade'
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject: RE: NRN Calls-Phototherapy Call

Reminder for today's call:

Materials for this call are attached to the email.

The SUPPORT call has been scheduled for

Wednesday, October 7th
SUPPORT 10:30-11:30am ET

For all calls please dial

Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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Extended Follow-up visit battery August 2009
School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

Test/questionnaire	Estimated time AGE RANGE	Spanish version?
ASSESSMENTS		
Check in: Wt, Ht, HC	~10 min	
WISC-IV	~45-60 min **6 yr 0 months – 16 yr 11 months**	YES http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&Mode=detail&Leaf=avpproducts
Movement-ABC –II	20-30 min **3-12 years**	Interpreter if needed http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308
Woodcock-Johnson III (ACH) **Letter-Word Identification** **Calculation**	~15 minutes **2 years -90+ years**	YES = "Bateria III" http://www.riverpub.com/products; http://www.riverpub.com/products/wjIIIAchievement/details.html
BREAK		
NEPSY II subtests ***Executive function domain*** **Auditory Attention/Response set** **Inhibition** ***Visuospatial domain*** **Design Copying** **Arrows** ***Memory*** **Memory for Names**	~25 min **Auditory Attention/Response (5-16 yrs); Inhibition (5-12); Design copying (3-16); Arrows (5-16); Memory for names (5-16)**	No
Neurologic exam	~15 min	Interpreter if needed
Functional *GMFCS* *Bimanual Fine Motor Function*	5 min **GMFCS – 6-12 yr** **BFMF – 4 yrs and older**	Interpreter if needed; http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf

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Extended Follow-up visit battery August 2009
School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

Test/questionnaire	Estimated time AGE RANGE	Spanish version?
PARENT QUESTIONNAIRES		
Medical history/SES/living arrangement	15 min	Interpreter if needed
QUICCC-R	5-10 min **2-18 years**	YES; http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF
PedsQL (Parent)	5-10 min **versions - 2-4 yrs, 5-7, 8-12, 13-18**	YES; http://www.pedsql.org/
Strengths and Difficulties Questionnaire (SDQ) (Parent)	5-10 min **version 4-10 yr**	YES; http://www.sdqinfo.com/
Conners Rating Scale (Parent) (ADHD or Short only)	10 min **6 yr-17 yr 11 months**	YES; http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&Mode=scoring&Leaf=Conners_3_SF#3
Social Communication Questionnaire (Parent; Lifetime form)	10 min **Over 4 years**	YES; http://portal.wpspublish.com/portal/page?_pageid=53,70432&_dad=portal&_schema=PORTAL
Behavior Rating Inventory of Executive Function (BRIEF-Parent)	15 min **5-18 yrs**	YES; http://www3.parinc.com/products/product.aspx?Productid=BRIEF

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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hensman, Angelita
Subject: RE: NEOProm meta analysis of oximetry trials
Date: Wednesday, October 07, 2009 10:09:15 AM

I am for this but sounds like we will need to get IRB approval for our data to be used. Tx, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 12:54 PM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,

Lisa Askie, who is leading the prospective meta analysis of the oximetry trials for which we are participating from the SUPPORT Trial is asking for birth order and sibling match to be included in the final data set. We do have information on birth order and sibling match in our data; however, there is a question of whether we can share that information due to privacy issues. For example, if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-3790 (FAX)
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From: Huitema, Carolyn Petrie
To: Huitema, Carolyn Petrie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Wallace, Dennis; Wally Carlo, M.D.; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Rich, Wade
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie
Subject: RE: NRN Calls-SUPPORT Call
Date: Wednesday, October 07, 2009 9:29:40 AM

Please note that the previous email is for SUPPORT, not Phototherapy as in the subject line.

From: Huitema, Carolyn Petrie
Sent: Wednesday, October 07, 2009 9:26 AM
To: 'Finer, Neil'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Poole, W. Kenneth; Wallace, Dennis; 'Wally Carlo, M.D.'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger.Faix@hsc.utah.edu'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'kurt.schibler@cchmc.org'; 'nancy newman'; 'Rich, Wade'
Cc: Irene, Amanda; Cunningham, Meg; Zaterka-Baxter, Kristin; Webb, Robin E.; Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject: RE: NRN Calls-Phototherapy Call

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For all calls please dial

Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From: Wally Carlo, M.D.
To: Cunningham, Meg
Cc: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; Finer, Neil
Subject: RE: SUPPORT Call
Date: Wednesday, October 07, 2009 7:42:23 AM
Attachments: Oxygen Saturation Target.10.01.09.doc

Hi Meg:

Enclosed is the most recent version of the O2 sat paper which you can circulate.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 06, 2009 8:14 PM
To: Cunningham, Meg
Cc: Wally Carlo, M.D.; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; 'adas@rti.org'; 'mgantz@rti.org'
Subject: RE: SUPPORT Call

Hi Meg
Please circulate this manuscript and Tables and ask Wally to send his most current version.
Thanks
Neil

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, October 06, 2009 8:46 AM
To: Finer, Neil
Cc: Martinez, Fernando; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: SUPPORT Call

Hi Dr. Finer,

Do you have an agenda or any materials to distribute before the call tomorrow? If so, please send them to me so I can distribute.

Thanks,
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837

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fax: 202-728-2095
www.rti.org

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10/01/09
5.0

The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

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525 New Hillman Building

619 South 20th Street

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Phone: (205) 934 4680

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Email: wcarlo@peds.uab.edu

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Word count:

Abstract: 93

Manuscript: 1921

Running head: Oxygen saturation and outcomes of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the NICHD Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death. As part of the SUPPORT Trial, infants were also randomized to continuous positive end expiratory pressure with permissive hypercapnia or to intubation and surfactant.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to also increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[14]

Pulse oximetry allows clinicians to utilize continuous oxygen saturations to target oxygenation in infants receiving oxygen supplementation. A survey study of 144 neonatal intensive care units conducted in 2001 revealed that the average lower limit of target oxygen saturations was 90% and the upper limit was 96%.[5] In recent years, the use of high saturation targets has been associated with the increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%) or $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%).[5] Oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy.[3] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was 27% in units

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where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects, including the possibility of increased risk of death with lower oxygenation as previously reported.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and ventilation strategy. The oxygen saturation arm tested the effect of a lower oxygen saturation target range (85-89%) compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. The ventilation arm of this factorial design trial also allowed us to simultaneously test the effect of prophylactic/early surfactant versus continuous positive airway pressure with a permissive ventilatory strategy on bronchopulmonary dysplasia or death at 36 weeks postmenstrual age (results to be reported separately). The factorial design of the trial effectively controlled for ventilator approaches in the oxygen saturation arm of this trial.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle Institute International, the independent Data Coordinating Center for the NRN (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age, without a decision to forego resuscitation were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiple births were randomized to the same arm of the trial.

Enrollment and treatment

Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). They were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95%. Deliveries were randomized as a unit; thus, multiples were randomized to the same arm of the trial. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% (Massimo Radical Set Pulse Oximeter, Irvine, CA) as previously used to separate oxygen saturations in premature infants.[20] The oxygen saturation values displayed reverted to actual values when less than 85% or higher than 95%, the levels of alarm setting recommendations by protocol. Oxygen saturation targeting with altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse

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oximetry. Adjustments in supplemental oxygen to maintain the target oxygen saturation between 88-92% were performed by the clinicians not by the research staff. For the ventilation arm of this 2 by 2 factorial design trial, participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge or 120 days postnatal age whichever occurred first. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, vitrectomy, and bevacizumab (Avastin). Outcomes included predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing incidence rates for infants in each treatment group (lower versus higher oxygen saturations) who

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developed the primary outcome. The model produces relative risk estimates adjusted for stratification by center and gestational age as well as for the familial clustering due to randomization of multiple births to the same treatment arm.

An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1310 infants for 80% power to detect a 10% difference in outcome assuming a baseline estimated rate of 50% of death/threshold retinopathy/surgery. This sample size estimate included an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. While these sample size calculations allowed for the testing of two co-primary outcomes for the two intervention arms (oxygenation and ventilation) of this 2 by 2 factorial trial, the trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent data safety and monitoring committee appointed by the Director of the NICHD reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

RESULTS

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1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily paused after evaluation by the Data Safety and Monitoring Committee (DSMC) and decision of the NICHD Director because of concerns regarding compliance with oxygen saturation targets. Separate analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and trial enrollment resumed upon approval by DSMC and NICHD Director decision. The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The Data Safety and Monitoring Committee masked interim analyses for safety were made available to the investigators after initial data analyses (last infant reached 55 weeks corrected age). There had been a trend for increased mortality in one of the treatment groups that had not reached the stopping boundary. The principal investigators and the NICHD and data center staff performed a detailed analysis which uncovered clinically and statistically significant trends with respect to mortality. While acknowledging that the designated primary outcome for this trial is death or retinopathy of prematurity, it was decided not to wait for incoming retinopathy of prematurity outcome data (which will take substantially more time to collect and assess) and report the mortality findings to the practicing neonatal community while the retinopathy of prematurity data accumulate. Retinopathy and 18-22 month follow up outcomes will be reported later.

Mortality at any time during hospitalization occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed within both gestational age

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groups used for stratification. Mortality in the first and second weeks after birth was comparable in the two treatment groups (Table 2). Other pre-specified major outcomes were comparable between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was some overlap (Figure 2). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not being based on randomized controlled trials and limited evidence of safety, lower oxygen saturation targeting has been increasingly adopted by units and physicians who are desirous of decreasing significant retinopathy of prematurity. However, in the current trial, lower oxygen saturation targeting (actual 85-89%) resulted in an increased risk of mortality.

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This trial was not powered for a difference in mortality only between the two oxygen saturation groups. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting, and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction among the outcomes evaluated. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence rather than from randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the trials from the1950s was a 4.9% increase in mortality in the oxygen restricted group, which is very similar to the 4% mortality increase in the lower targeted SpO2 group that was observed in our trial.[1]

Restriction of oxygenation in previous randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group. Mortality in the current trial did not differ by 7 or 14 days. Therefore, we surmise that the lower target of oxygen saturations rather than the postnatal age of the intervention is related to the adverse outcome.

There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[1] At the present time, it is important that these trials continue and that the investigators and the data safety and monitoring committees of these trials are

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aware of the results of the current trial so that appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies, such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no. (%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Adjusted Relative Risk[1] (95% CI)
Death before discharge	130/655 (20)	106/661 (16)	
Death by 7 days	41/655 (6)	38/661 (6)	
Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	

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Pneumothorax – no. (%)	48/655 (7)	43/661 (7)
Any air leaks – no. (%)	50/655 (8)	43/661 (7)
Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

[1]Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

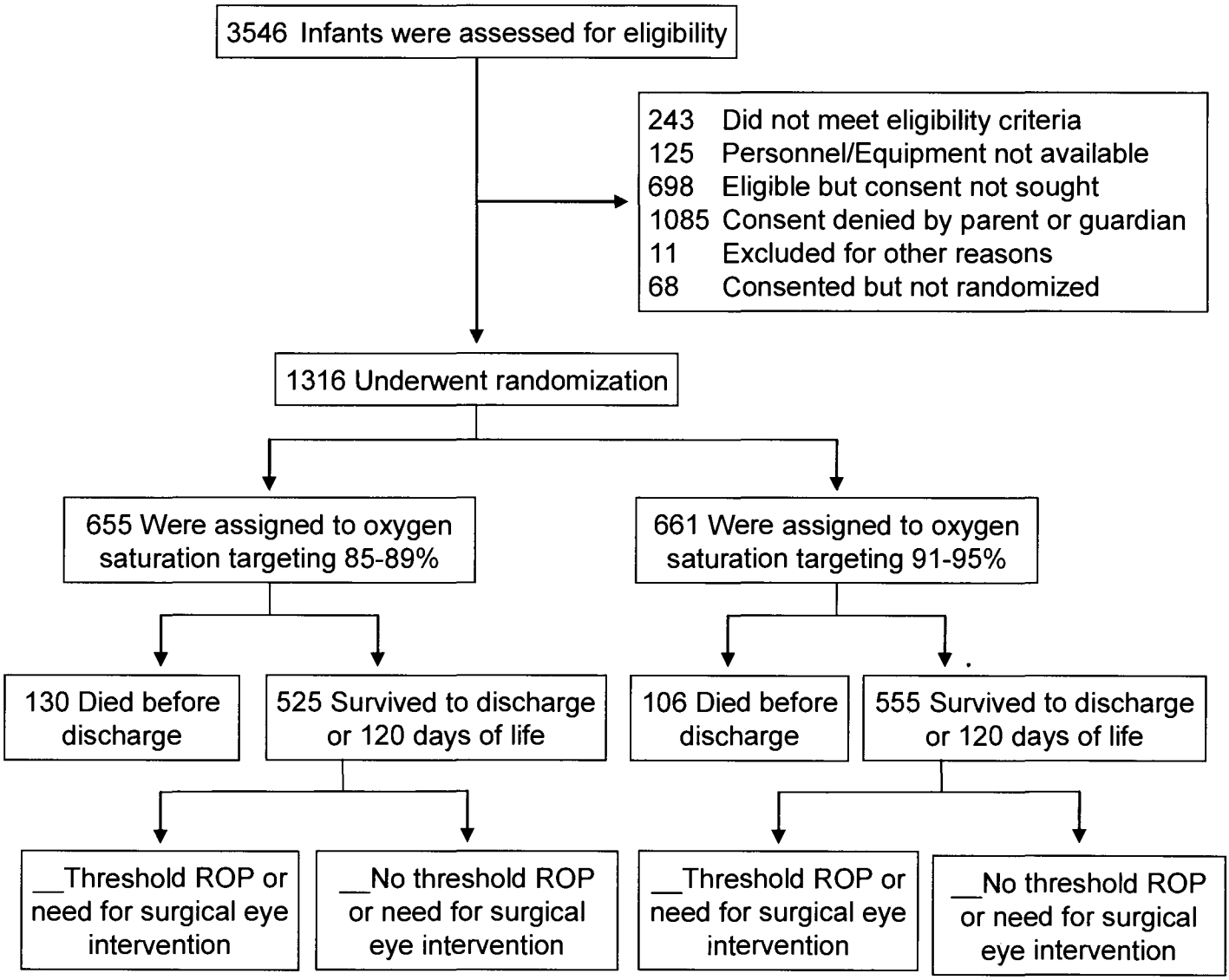

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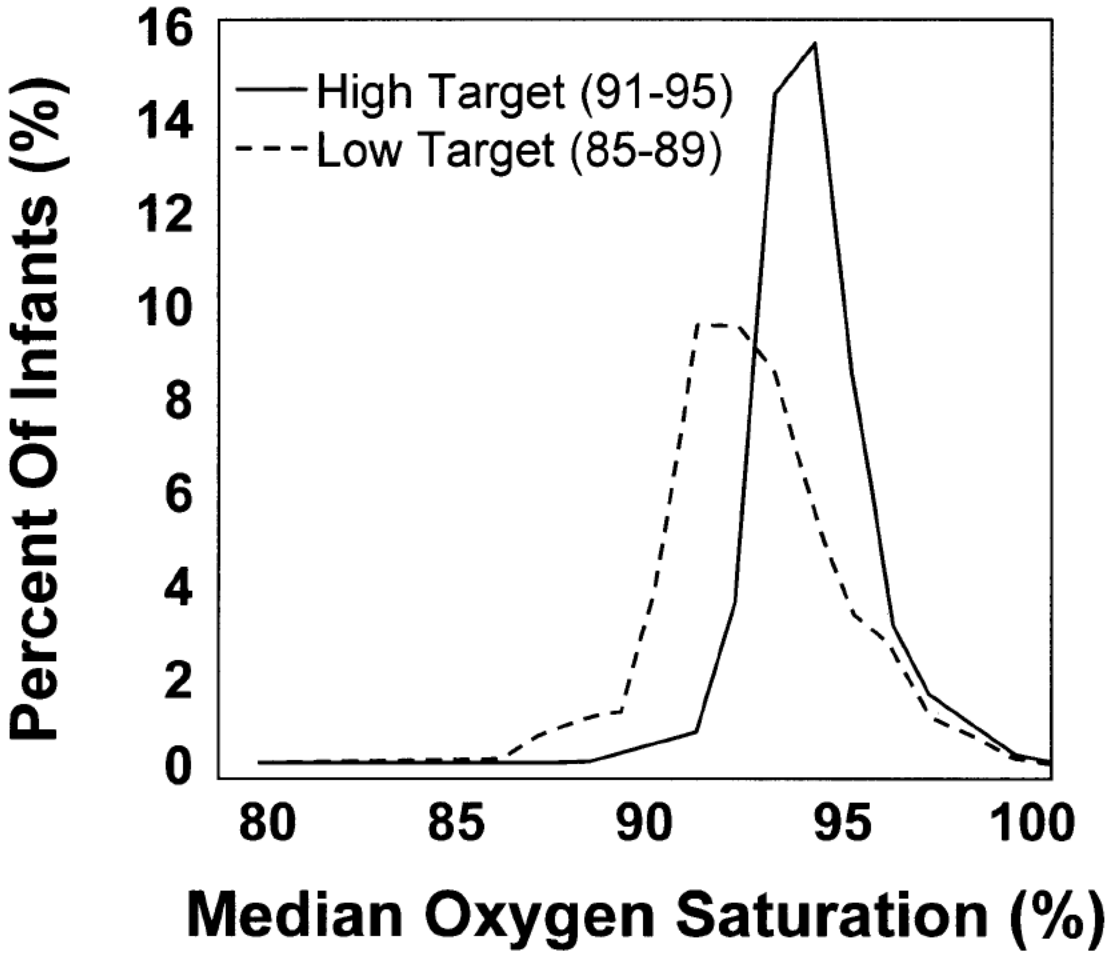
Figure 2



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From:	Finer, Neil
To:	Cunningham, Meg
Cc:	wcarlo@peds.uab.edu; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; "adas@rti.org"; "mgantz@rti.org"
Subject:	RE: SUPPORT Call
Date:	Tuesday, October 06, 2009 9:13:49 PM
Attachments:	SUPPORT CPAP vs Surf Oct 06 09 .docx Tables Aug 29.docx T3 BPD Outcomes with adj tests - PRELIMINARY 08-21-09.rtf T1 Patient Description - PRELIMINARY 08-23-09.rtf T2 Other Outcomes - PRELIMINARY 08-24-09.rtf

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Thanks

Neil

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, October 06, 2009 8:46 AM
To: Finer, Neil
Cc: Martinez, Fernando; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: SUPPORT Call

Hi Dr. Finer,

Do you have an agenda or any materials to distribute before the call tomorrow? If so, please send them to me so I can distribute.

Thanks,
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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1317 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group (all p<0.001), and 67% of the CPAP infants received surfactant at any time during their hospitalization,. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, p=0.03). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants requiring intubation during their nursery course, (p<0.001). There were no differences between the groups for air leaks including pneumothoraces.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months.

Comment [AD1]: Should we rephrase this? Sounds like the infants themselves gave consent!

Comment [AD2]: I would provide the relative risk and 95% CI instead of, or in addition to the p value. Same goes for other CPAP vs surfactant outcome comparisons, both here and in the main text.

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Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation

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or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses~~6~~, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an **increased survival without BPD** at 36 weeks.

Comment [AD3]: We should be consistent in either picking death or BPD, or survival without BPD.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized within each center to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by center and gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), **and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%**. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by a further 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

Comment [AD4]: Since we are not reporting NDI here, and did not adjust our sample size for multiple outcomes, do we need to say this?

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks. Adjustment was performed as pre-specified for gestational age, center and familial clustering using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risks. A two-sided P value of less than 0.05 was considered statistically significant. An independent data safety monitoring committee reviewed the interim safety and efficacy results, including those concerning adverse outcomes, four times. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety and efficacy monitoring. Safety outcomes monitored included death, pneumothorax, intraventricular hemorrhage and a combination of any of the above events.

Comment [AD5]: Let us make the statistical sections of both primary papers as similar as possible.

The study was approved by Human Subjects Committees at all participating sites and RTI, the NRN data center that managed and analyzed all the data, and parental consent for participation in the trial was required before delivery.

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Results:

There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 treatment groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, $p=0.27$. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (40% vs 41%, $p=0.96$), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, $p=0.32$).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.01$). There were no differences between the groups in air leaks in the first 14 days, air leaks during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, $p<.001$).

Strata Results: 24 – 25 weeks Gestation

Comment [AD6]: Do we need to preface some justification for looking within strata?

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There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p<0.01, lesser days of mechanical ventilation, 10.7 vs 14.2, p<0.01, and less postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[1414] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.**~~8~~ We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. We also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe

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that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0552

Table 2. Delivery Room interventions

Variable	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Apgar at 1 minute <3	23% (154/662)	26% (167/652)	0.3214
Apgar at 5 minutes <3	4% (26/664)	5% (32/652)	0.3806
PPV in the DR (per SUPP03)	66% (435/662)	93% (605/651)	<0.0001*
CPAP in the DR (per SUPP03)	81% (539/663)	22% (146/652)	<0.0001*
Surfactant in DR (per SUPP03)	14% (93/659)	51% (334/651)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)	67% (443/660)	99% (645/652)	<0.0001*
Chest compressions in DR (per SUPP03)	5% (36/660)	6% (40/652)	0.5978
Epinephrine in DR (per SUPP03)	2% (13/660)	4% (27/652)	0.0222*
Death in the DR (per SUPP03/SUPP04)	0% (1/663)	1% (6/652)	0.0552

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9797
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	99.9 ± 42.6	100.5 ± 39.4	0.8210
Days on supplemental oxygen (survivors only)	53.9 ± 37.2	57.4 ± 37.0	0.1138
Days on mechanical vent (HFV & CV) (survivors only)	19.0 ± 22.8	22.0 ± 24.8	0.0392*
Days on CPAP (survivors only)	16.1 ± 13.2	16.0 ± 14.6	0.9229
Discharge on oxygen	22% (120/547)	24% (121/514)	0.5334
Alive and off MV (HFV/CV) at 7 days	55% (362/654)	49% (316/650)	0.0149*
Any air leak in first 14 days	7% (44/664)	8% (49/652)	0.5293
Medical or surgical NEC	13% (83/655)	10% (62/634)	0.1004
PDA requiring surgery	11% (73/654)	11% (68/634)	0.8019
IVH grade 3-4	15% (95/644)	13% (80/627)	0.3027
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0004*

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/279)	0.5127
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.0 ± 47.4	118.6 ± 39.6	0.7514
Days on supplemental oxygen (survivors only)	75.7 ± 34.1	76.8 ± 33.1	0.7500
Days on mechanical vent (HFV & CV) (survivors only)	32.1 ± 26.6	35.8 ± 27.8	0.1672
Days on CPAP (survivors only)	18.6 ± 13.9	17.7 ± 15.5	0.5496
Discharge on oxygen	32% (68/212)	31% (57/185)	0.7867
Alive and off MV (HFV/CV) at 7 days	34% (97/282)	26% (73/279)	0.0339*
Any air leak in first 14 days	8% (22/285)	10% (28/280)	0.3399
Medical or surgical NEC	15% (42/279)	13% (34/267)	0.4338
PDA requiring surgery	16% (46/279)	18% (47/267)	0.7289
IVH grade 3-4	19% (53/273)	19% (50/265)	0.8722
Postnatal steroids for BPD	13% (36/276)	21% (54/263)	0.0198*

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Table 3: BPD outcomes for High vs. Low SpO2
*****PRELIMINARY DATA*****

Characteristic	High SpO2 (N=664)	Low SpO2 (N=652)	Unadjusted p-value	Adjusted p-value
Death by 36 weeks PMA	14% (94/664)	17% (114/652)	0.0980	0.1046
BPD (physiologic definition)	39% (225/570)	41% (220/538)	0.6302	0.8269
Death or BPD (physiologic definition) by 36 weeks	48% (319/664)	51% (334/652)	0.2480	0.2890
BPD (supplemental O2)	40% (227/570)	44% (239/538)	0.1211	0.2142
Death or BPD (supplemental oxygen) by 36 weeks	48% (321/664)	54% (353/652)	0.0354*	0.0424*

Characteristic	High SpO2 (N=661)	Low SpO2 (N=655)	Unadjusted p-value	Adjusted p-value
Death by 36 weeks PMA	14% (94/661)	17% (114/655)	0.1134	0.0821
BPD (physiologic definition)	42% (238/567)	38% (207/541)	0.2076	0.2345
Death or BPD (physiologic definition) by 36 weeks	50% (332/661)	49% (321/655)	0.6583	0.8597
BPD (supplemental O2)	46% (262/567)	38% (204/541)	0.0042*	0.0026*
Death or BPD (supplemental oxygen) by 36 weeks	54% (356/661)	49% (318/655)	0.0541	0.0830

† Adjusted p-values are adjusted for stratification by GA and center and familial clustering.

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Table 1. Patient Description for CPAP vs. Surfactant

PRELIMINARY DATA

GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Apgar at 1 minute <3		23% (154/662)	26% (167/652)	0.3214
Apgar at 5 minutes <3		4% (26/664)	5% (32/652)	0.3806
PPV in the DR (per SUPP03)		66% (435/662)	93% (605/651)	<0.0001*
CPAP in the DR (per SUPP03)		81% (539/663)	22% (146/652)	<0.0001*
Surfactant in DR (per SUPP03)		14% (93/659)	51% (334/651)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		67% (443/660)	99% (645/652)	<0.0001*
Chest compressions in DR (per SUPP03)		5% (36/660)	6% (40/652)	0.5978
Epinephrine in DR (per SUPP03)		2% (13/660)	4% (27/652)	0.0222*
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0552

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

		CPAP (N=285)		
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (105/280)	0.0414*
	Non-Hispanic White	32% (92/285)	43% (121/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.4 ± 139.5	0.0718
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1110
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (per SUPP03)		73% (206/283)	95% (267/280)	<0.0001*
CPAP in the DR (per SUPP03)		72% (205/284)	22% (62/280)	<0.0001*
Surfactant in DR (per SUPP03)		21% (59/283)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		77% (219/283)	99% (276/280)	<0.0001*
Chest compressions in DR (per SUPP03)		10% (27/284)	8% (23/280)	0.5892
Epinephrine in DR (per SUPP03)		4% (10/284)	5% (15/280)	0.2895
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (per SUPP03/SUPP04)		0% (1/284)	1% (4/280)	0.1727

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Table 1. Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Male		51% (195/379)	56% (208/372)	0.2201
Race/ethnicity	Non-Hispanic Black	35% (133/379)	35% (129/372)	0.8629
	Non-Hispanic White	42% (158/379)	40% (150/372)	
	Hispanic	20% (75/379)	20% (76/372)	
	Other/unknown	3% (13/379)	5% (17/372)	
Birth weight (grams)	Mean (n=751)	922.4 ± 180.4	921.3 ± 181.5	0.9381
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.8832
Apgar at 1 minute <3		17% (66/378)	22% (83/372)	0.0959
Apgar at 5 minutes <3		2% (7/379)	3% (13/372)	0.1609
PPV in the DR (per SUPP03)		60% (229/379)	91% (338/371)	<0.0001*
CPAP in the DR (per SUPP03)		88% (334/379)	23% (84/372)	<0.0001*
Surfactant in DR (per SUPP03)		9% (34/376)	50% (185/371)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		59% (224/377)	99% (369/372)	<0.0001*
Chest compressions in DR (per SUPP03)		2% (9/376)	5% (17/372)	0.1042
Epinephrine in DR (per SUPP03)		1% (3/376)	3% (12/372)	0.0179*
Antenatal steroids (any)		96% (364/379)	94% (351/372)	0.2792
Antenatal steroids (full course)		70% (262/376)	68% (250/370)	0.5340
Death in the DR (per SUPP03/SUPP04)		0% (0/379)	1% (2/372)	0.1529

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Table 1. Patient Description for High vs. Low SpO2

*****PRELIMINARY DATA*****

GA (weeks)	24-25	43% (287/661)	42% (278/655)	0.7205
	26-27	57% (374/661)	58% (377/655)	
Male		56% (370/661)	52% (342/655)	0.1709
Race/ethnicity	Non-Hispanic Black	35% (231/661)	39% (258/655)	0.2398
	Non-Hispanic White	42% (279/661)	37% (242/655)	
	Hispanic	19% (127/661)	20% (132/655)	
	Other/unknown	4% (24/661)	4% (23/655)	
Birth weight (grams)	Mean (n=1316)	825.3 ± 193.2	835.3 ± 193.3	0.3464
Gestational age at birth (weeks)	Mean (n=1316)	26.1 ± 1.1	26.2 ± 1.1	0.4635
Apgar at 1 minute <3		26% (169/661)	23% (152/653)	0.3340
Apgar at 5 minutes <3		4% (24/661)	5% (34/655)	0.1680
PPV in the DR (per SUPP03)		81% (532/660)	78% (508/653)	0.2095
CPAP in the DR (per SUPP03)		52% (345/661)	52% (340/654)	0.9404
Surfactant in DR (per SUPP03)		34% (227/658)	31% (200/652)	0.1399
Surfactant in DR or NICU (per SUPP03 & SUPP04)		85% (557/659)	81% (531/653)	0.1229
Chest compressions in DR (per SUPP03)		6% (38/661)	6% (38/651)	0.9454
Epinephrine in DR (per SUPP03)		3% (21/661)	3% (19/651)	0.7855
Antenatal steroids (any)		96% (631/660)	97% (634/655)	0.2601
Antenatal steroids (full course)		70% (460/657)	73% (478/652)	0.1856
Death in the DR (per SUPP03/SUPP04)		1% (4/661)	0% (3/654)	0.7152

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Table 1. Patient Description for High vs. Low SpO2
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

Male		59% (169/287)	50% (140/278)	0.0418*
Race/ethnicity	Non-Hispanic Black	37% (105/287)	44% (122/278)	0.0841
	Non-Hispanic White	41% (118/287)	34% (95/278)	
	Hispanic	18% (52/287)	20% (56/278)	
	Other/unknown	4% (12/287)	2% (5/278)	
Birth weight (grams)	Mean (n=565)	711.2 ± 134.1	705.7 ± 131.1	0.6229
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.1 ± 0.6	0.5523
Apgar at 1 minute <3		30% (87/287)	31% (85/277)	0.9235
Apgar at 5 minutes <3		6% (16/287)	8% (22/278)	0.2672
PPV in the DR (per SUPP03)		86% (246/286)	82% (227/277)	0.1883
CPAP in the DR (per SUPP03)		49% (140/287)	46% (127/277)	0.4857
Surfactant in DR (per SUPP03)		40% (114/286)	34% (94/277)	0.1453
Surfactant in DR or NICU (per SUPP03 & SUPP04)		91% (259/286)	85% (236/277)	0.0510
Chest compressions in DR (per SUPP03)		9% (26/287)	9% (24/277)	0.8690
Epinephrine in DR (per SUPP03)		6% (16/287)	3% (9/277)	0.1797
Antenatal steroids (any)		97% (277/286)	98% (273/278)	0.3035
Antenatal steroids (full course)		74% (211/285)	77% (215/278)	0.3612
Death in the DR (per SUPP03/SUPP04)		1% (3/287)	1% (2/277)	0.6822

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Table 1, Patient Description for High vs. Low SpO2
Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Male		54% (201/374)	54% (202/377)	0.9644
Race/ethnicity	Non-Hispanic Black	34% (126/374)	36% (136/377)	0.5294
	Non-Hispanic White	43% (161/374)	39% (147/377)	
	Hispanic	20% (75/374)	20% (76/377)	
	Other/unknown	3% (12/374)	5% (18/377)	
Birth weight (grams)	Mean (n=751)	912.8 ± 185.9	930.9 ± 175.4	0.1712
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.5568
Apgar at 1 minute <3		22% (82/374)	18% (67/376)	0.1588
Apgar at 5 minutes <3		2% (8/374)	3% (12/377)	0.3743
PPV in the DR (per SUPP03)		76% (286/374)	75% (281/376)	0.5798
CPAP in the DR (per SUPP03)		55% (205/374)	56% (213/377)	0.6419
Surfactant in DR (per SUPP03)		30% (113/372)	28% (106/375)	0.5265
Surfactant in DR or NICU (per SUPP03 & SUPP04)		80% (298/373)	78% (295/376)	0.6286
Chest compressions in DR (per SUPP03)		3% (12/374)	4% (14/374)	0.6897
Epinephrine in DR (per SUPP03)		1% (5/374)	3% (10/374)	0.1922
Antenatal steroids (any)		95% (354/374)	96% (361/377)	0.4791
Antenatal steroids (full course)		67% (249/372)	70% (263/374)	0.3190
Death in the DR (per SUPP03/SUPP04)		0% (1/374)	0% (1/377)	0.9955

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Table 2: Other outcomes for CPAP vs. Surfactant

*****PRELIMINARY DATA*****

Death in the first week		6% (40/664)	6% (39/651)	0.9797
Death at any time while hospitalized		16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	Mean (n=1064)	99.9 ± 42.6	100.5 ± 39.4	0.8210
LOS in NRN hospital (survivors only)	Mean (n=1070)	97.4 ± 43.3	96.5 ± 41.0	0.7316
Days on supplemental oxygen (survivors only)	Mean (n=1078)	53.9 ± 37.2	57.4 ± 37.0	0.1138
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=1078)	19.0 ± 22.8	22.0 ± 24.8	0.0392*
Days on CPAP (survivors only)	Mean (n=1078)	16.1 ± 13.2	16.0 ± 14.6	0.9229
Days on nasal SIMV (survivors only)	Mean (n=1078)	3.4 ± 6.8	3.5 ± 6.9	0.7898
Discharge on oxygen		22% (120/547)	24% (121/514)	0.5334
Alive and off MV (HFV/CV) at 7 days		55% (362/654)	49% (316/650)	0.0149*
Pneumothorax (NG03 or SUPP08)		8% (54/664)	6% (36/652)	0.0606
Any air leak on SUPP08 in first 14 days		7% (44/664)	8% (49/652)	0.5293
Medical or surgical NEC		13% (83/655)	10% (62/634)	0.1004
PDA requiring surgery		11% (73/654)	11% (68/634)	0.8019
IVH grade 3-4 (NG03, SUPP08, SUPP09)		15% (95/644)	13% (80/627)	0.3027
Postnatal steroids for BPD		7% (47/650)	13% (83/629)	0.0004*
Intubated in DR or NICU (SUPP03 & SUPP04)		77% (508/661)	100% (648/651)	<0.0001*

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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Table 2: Other outcomes for CPAP vs. Surfactant
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

Clinical Outcome	Category	CPAP (N=285)	SURF (N=279)	p-value
Death in the first week		9% (25/285)	10% (29/279)	0.5127
Death at any time while hospitalized		24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	Mean (n=400)	120.0 ± 47.4	118.6 ± 39.6	0.7514
LOS in NRN hospital (survivors only)	Mean (n=402)	117.3 ± 46.7	116.1 ± 42.5	0.7946
Days on supplemental oxygen (survivors only)	Mean (n=406)	75.7 ± 34.1	76.8 ± 33.1	0.7500
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=406)	32.1 ± 26.6	35.8 ± 27.8	0.1672
Days on CPAP (survivors only)	Mean (n=406)	18.6 ± 13.9	17.7 ± 15.5	0.5496
Days on nasal SIMV (survivors only)	Mean (n=406)	5.1 ± 8.1	5.4 ± 8.2	0.7156
Discharge on oxygen		32% (68/212)	31% (57/185)	0.7867
Alive and off MV (HFV/CV) at 7 days		34% (97/282)	26% (73/279)	0.0339*
Pneumothorax (NG03 or SUPP08)		10% (29/285)	8% (21/280)	0.2629
Any air leak on SUPP08 in first 14 days		8% (22/285)	10% (28/280)	0.3399
Medical or surgical NEC		15% (42/279)	13% (34/267)	0.4338
PDA requiring surgery		16% (46/279)	18% (47/267)	0.7289
IVH grade 3-4 (NG03, SUPP08, SUPP09)		19% (53/273)	19% (50/265)	0.8722
Postnatal steroids for BPD		13% (36/276)	21% (54/263)	0.0198*
Intubated in DR or NICU (SUPP03 & SUPP04)		88% (249/284)	99% (278/280)	<0.0001*

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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Table 2 Other outcomes for CPAP vs. Surfactant
Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Death in the first week		4% (15/379)	3% (10/372)	0.3322
Death at any time while hospitalized		11% (41/379)	10% (37/372)	0.6954
Total LOS any hospital (survivors only)	Mean (n=664)	87.2 ± 33.6	90.2 ± 35.4	0.2515
LOS in NRN hospital (survivors only)	Mean (n=668)	84.7 ± 35.6	85.5 ± 35.8	0.7729
Days on supplemental oxygen (survivors only)	Mean (n=672)	39.8 ± 31.9	46.5 ± 34.6	0.0097*
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=672)	10.7 ± 14.9	14.2 ± 19.0	0.0068*
Days on CPAP (survivors only)	Mean (n=672)	14.5 ± 12.5	15.1 ± 14.0	0.5878
Days on nasal SIMV (survivors only)	Mean (n=672)	2.3 ± 5.6	2.5 ± 5.8	0.7618
Discharge on oxygen		16% (52/335)	19% (64/329)	0.1823
Alive and off MV (HFV/CV) at 7 days		71% (265/372)	65% (243/371)	0.0926
Pneumothorax (NG03 or SUPP08)		7% (25/379)	4% (15/372)	0.1177
Any air leak on SUPP08 in first 14 days		6% (22/379)	6% (21/372)	0.9250
Medical or surgical NEC		11% (41/376)	8% (28/367)	0.1241
PDA requiring surgery		7% (27/375)	6% (21/367)	0.4132
IVH grade 3-4 (NG03, SUPP08, SUPP09)		11% (42/371)	8% (30/362)	0.1677
Postnatal steroids for BPD		3% (11/374)	8% (29/366)	0.0027*
Intubated in DR or NICU (SUPP03 & SUPP04)		69% (259/377)	100% (370/371)	<0.0001*

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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Table 2: Other outcomes for High vs. Low SpO2

*****PRELIMINARY DATA*****

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death in the first week		6% (38/660)	6% (41/655)	0.7017
Death at any time while hospitalized		16% (106/660)	20% (130/655)	0.0736
Total LOS any hospital (survivors only)	Mean (n=1064)	101.9 ± 43.3	98.4 ± 38.6	0.1698
LOS in NRN hospital (survivors only)	Mean (n=1070)	99.1 ± 43.5	94.7 ± 40.7	0.0928
Days on supplemental oxygen (survivors only)	Mean (n=1078)	59.9 ± 36.2	51.0 ± 37.5	<0.0001*
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=1078)	21.6 ± 24.2	19.4 ± 23.4	0.1322
Days on CPAP (survivors only)	Mean (n=1078)	16.1 ± 14.1	16.0 ± 13.6	0.9820
Days on nasal SIMV (survivors only)	Mean (n=1078)	3.8 ± 7.2	3.1 ± 6.4	0.0689
Discharge on oxygen		23% (126/543)	22% (115/518)	0.6965
Alive and off MV (HFV/CV) at 7 days		50% (327/656)	54% (351/648)	0.1186
Pneumothorax (NG03 or SUPP08)		6% (42/661)	7% (48/655)	0.4839
Any air leak on SUPP08 in first 14 days		7% (43/661)	8% (50/655)	0.4245
Medical or surgical NEC		11% (69/647)	12% (76/642)	0.5050
PDA requiring surgery		11% (68/646)	11% (73/642)	0.6275
IVH grade 3-4 (NG03, SUPP08, SUPP09)		13% (82/639)	15% (93/632)	0.3301
Postnatal steroids for BPD		11% (68/642)	10% (62/637)	0.6113
Intubated in DR or NICU (SUPP03 & SUPP04)		89% (588/660)	87% (568/652)	0.2693

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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Table 2. Other outcomes for High vs. Low SpO2
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Death in the first week		10% (28/286)	9% (26/278)	0.8598
Death at any time while hospitalized		26% (73/286)	31% (85/278)	0.1817
Total LOS any hospital (survivors only)	Mean (n=400)	120.0 ± 45.8	118.6 ± 41.7	0.7587
LOS in NRN hospital (survivors only)	Mean (n=402)	117.9 ± 46.5	115.4 ± 42.8	0.5780
Days on supplemental oxygen (survivors only)	Mean (n=406)	79.8 ± 30.2	72.2 ± 36.7	0.0233*
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=406)	34.2 ± 27.2	33.4 ± 27.3	0.7701
Days on CPAP (survivors only)	Mean (n=406)	19.3 ± 15.8	16.9 ± 13.1	0.0866
Days on nasal SIMV (survivors only)	Mean (n=406)	5.6 ± 8.5	4.7 ± 7.6	0.2563
Discharge on oxygen		33% (69/208)	30% (56/189)	0.4477
Alive and off MV (HFV/CV) at 7 days		28% (79/286)	33% (91/275)	0.1589
Pneumothorax (NG03 or SUPP08)		7% (20/287)	11% (30/278)	0.1097
Any air leak on SUPP08 in first 14 days		7% (20/287)	11% (30/278)	0.1097
Medical or surgical NEC		13% (37/275)	14% (39/271)	0.7519
PDA requiring surgery		16% (44/275)	18% (49/271)	0.5178
IVH grade 3-4 (NG03, SUPP08, SUPP09)		19% (51/273)	20% (52/265)	0.7814
Postnatal steroids for BPD		16% (43/271)	18% (47/268)	0.6032
Intubated in DR or NICU (SUPP03 & SUPP04)		95% (272/287)	92% (255/277)	0.1928

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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Table 2: Other outcomes for High vs. Low SpO2
Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Death in the first week		3% (10/374)	4% (15/377)	0.3189
Death at any time while hospitalized		9% (33/374)	12% (45/377)	0.1621
Total LOS any hospital (survivors only)	Mean (n=664)	90.6 ± 37.6	86.8 ± 31.1	0.1542
LOS in NRN hospital (survivors only)	Mean (n=668)	87.3 ± 37.0	82.8 ± 34.2	0.1046
Days on supplemental oxygen (survivors only)	Mean (n=672)	47.4 ± 34.1	38.7 ± 32.2	0.0007*
Days on mechanical vent (HFV & CV) (survivors only)	Mean (n=672)	13.7 ± 18.2	11.2 ± 15.9	0.0604
Days on CPAP (survivors only)	Mean (n=672)	14.0 ± 12.5	15.6 ± 13.9	0.1309
Days on nasal SIMV (survivors only)	Mean (n=672)	2.7 ± 6.0	2.1 ± 5.4	0.1813
Discharge on oxygen		17% (57/335)	18% (59/329)	0.7554
Alive and off MV (HFV/CV) at 7 days		67% (248/370)	70% (260/373)	0.4325
Pneumothorax (NG03 or SUPP08)		6% (22/374)	5% (18/377)	0.4991
Any air leak on SUPP08 in first 14 days		6% (23/374)	5% (20/377)	0.6184
Medical or surgical NEC		9% (32/372)	10% (37/371)	0.5198
PDA requiring surgery		6% (24/371)	6% (24/371)	1.0000
IVH grade 3-4 (NG03, SUPP08, SUPP09)		8% (31/366)	11% (41/367)	0.2191
Postnatal steroids for BPD		7% (25/371)	4% (15/369)	0.1078
Intubated in DR or NICU (SUPP03 & SUPP04)		85% (316/373)	83% (313/375)	0.6398

Table 2 missing postnatal age of oxygen, PVL and death/PVL, never intubated

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: NEOProm meta analysis of oximetry trials
Date: Tuesday, October 06, 2009 6:41:01 PM

Rosemary D. Higgins, MD
Program Scientist

From: Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>
To: Walsh, Michele <Michele.Walsh@uhhospitals.org>; Ellen Hale <Ellen.Hale@oz.ped.emory.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <nfiner@ucsd.edu>; Luc.Brion@UTSouthwestern.edu <Luc.Brion@UTSouthwestern.edu>; rohls@unm.edu <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; ambal@uab.edu <ambal@uab.edu>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; ifrantz@tuftsmedicalcenter.org <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Michelle Walsh <mcw3@po.cwru.edu>; MIckey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOldberg <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Cunningham, Meg <mcunningham@rti.org>
Sent: Tue Oct 06 18:38:06 2009
Subject: Re: NEOProm meta analysis of oximetry trials

I have sent a query to our IRB
I agree with Michele that this is important info and would like to be able to vote a YES without a restriction on higher order multiples
Will keep you posted when I get the IRB's response

BJS**"Walsh, Michele" <Michele.Walsh@uhhospitals.org> writes:**
I think it is very important that we provide the data on twins.

Because of the increasing information on the heritability of both ROP and

BPD, it is important for metanalyses to develop techniques to be able to

Account for this clustering by family unit, unless the babes are independently

Randomized. It is possible that to protect confidentiality we could withhold the data on higher

Multiples. I support giving the information.

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Michele Walsh

beeper (b) (6)

Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 12:54 PM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,

Lisa Askie, who is leading the prospective meta analysis of the oximetry trials for which we are participating from the SUPPORT Trial is asking for birth order and sibling match to be included in the final data set. We do have information on birth order and sibling match in our data, however, there is a question of whether we can share that information due to privacy issues. For example, if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

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Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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Federal and Ohio law protect patient medical information, including psychiatric disorders,

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(H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
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From: Gantz, Marie
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates
Date: Tuesday, October 06, 2009 5:18:58 PM
Attachments: SUPPORT enrollment by center 06OCT09.doc

Numbers on infants enrolled and eligible by center are attached. Note that I calculated the numbers in two ways. First, I looked at infants who met the SUPPORT inclusion criteria (inborn, 24-27 weeks GA, to receive full resuscitation, and no known major congenital malformations). Second, I looked at those who were "eligible" by subtracting those who met exclusion criteria (born during a time when personnel and/or equipment were unavailable) from those who met inclusion criteria. (In 119 out of the 125 cases where exclusion criteria were met it was because personnel were not available.) The numbers are similar for most centers, but there is a difference for a few, most notably Brown. I will leave it to others to decide which set of numbers are more reasonable to use for authorship order.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, October 06, 2009 4:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Marie,

If you can send me the numbers by site, I'll plug them into my spreadsheet.

Thanks,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 06, 2009 2:07 PM
To: 'mgantz@rti.org'; 'adas@rti.org'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Can we use the SUPP02 numbers? This is more accrate
Rosemary D. Higgins, MD

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Program Scientist

From: Gantz, Marie <mgantz@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>
Cc: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tue Oct 06 14:04:20 2009
Subject: RE: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Rose,

The numbers in the spreadsheet appear to come from the latest monthly report where the number eligible is calculated as described in the footnote:

Eligible GDB patients are those keyed in the NG02 (inborn and GA of 24 0/6 & 27 6/7) with a birth date after the first Support patient keyed for sites at each Center and not born on or between dates of Support study suspension 11/23/2005 and 2/5/2006.

As we have discussed before, these numbers do not match the numbers of infants on the SUPP02 which was supposed to be completed for "all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation" and which captures additional eligibility information. I would be inclined to use the SUPP02 numbers, but what do you think?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 11:41 AM
To: Gantz, Marie; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Marie/Abhik
Can you check our numbers to make sure we have the authorship order correct. Stephanie has put this together in order to move the papers along.

Thanks
Rose

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, October 06, 2009 9:56 AM
To: 'Finer, Neil'; Wally Carlo (wcarlo@peds.uab.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Ventilation and Oximetry papers | Author list and boilerplates

Hi Neil and Wally,

Attached are two files, one for the Ventilation and one for the Oximetry papers, with the

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authors lists and boilerplates. The boilerplates are identical for both papers. The author lists have a few variations for the Yale and Cincinnati authors, as well as switching your names around. Author affiliations are included as footnotes. If you need me to copy these into your drafts, please send the drafts to me.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
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Infants enrolled in SUPPORT, by center

Center ID number	Number enrolled per SUPP02	Number who met inclusion criteria per SUPP02	Percent of those who met inclusion criteria who were enrolled	Number eligible* per SUPP02	Percent of eligible* infants who were enrolled
3	107	212	50.5	212	50.5
4	73	163	44.8	148	49.3
5	68	179	38.0	179	38.0
8	17	32	53.1	32	53.1
9	86	206	41.7	205	42.0
11	91	375	24.3	371	24.5
12	74	225	32.9	214	34.6
13	37	156	23.7	153	24.2
14	124	257	48.2	226	54.9
15	56	125	44.8	125	44.8
16	184	399	46.1	385	47.8
18	85	233	36.5	209	40.7
19	65	149	43.6	145	44.8
20	9	20	45.0	20	45.0
21	8	8	100.0	8	100.0
22	74	108	68.5	107	69.2
23	57	94	60.6	94	60.6
24	29	96	30.2	89	32.6
25	52	185	28.1	181	28.7
26	21	82	25.6	76	27.6

***Eligible infants are those who met inclusion criteria and were born when personnel and equipment were available**

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org
Subject: RE: NEOProm meta analysis of oximetry trials
Date: Tuesday, October 06, 2009 4:16:25 PM

Out of 1317 infants we have:

4 sets of quadruplets (16 babies)
15 sets of triplets (45 babies)
132 sets of twins (264 babies)

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 2:44 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: Fw: NEOProm meta analysis of oximetry trials

Can you tell us how many sets of

Triplets
Quads
Quints
Rosemary D. Higgins, MD
Program Scientist

From: Frantz, Ivan <ifrantz@tuftsmedicalcenter.org>
To: Walsh, Michele <Michele.Walsh@UHhospitals.org>; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <nfiner@ucsd.edu>; Luc.Brion@UTSouthwestern.edu <Luc.Brion@UTSouthwestern.edu>; rohls@unm.edu <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; ambal@uab.edu <ambal@uab.edu>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Michelle Walsh <mcw3@po.cwru.edu>; MIckey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOldberg <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Cunningham, Meg <mcunningham@rti.org>
Sent: Tue Oct 06 14:41:20 2009
Subject: RE: NEOProm meta analysis of oximetry trials

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I agree with Michele that the information will be valuable, and her compromise may be the best solution. Before making a decision we need to know how many subjects fall into each group of multiples. With this information we will have a sense of how much the data will be compromised by eliminating a group and what the risk of identification is by including them.

Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, October 06, 2009 1:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Frantz, Ivan; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: RE: NEOProm meta analysis of oximetry trials

I think it is very important that we provide the data on twins.
Because of the increasing information on the heritability of both ROP and
BPD, it is important for metanalyses to develop techniques to be able to
Account for this clustering by family unit, unless the babes are independently
Randomized. It is possible that to protect confidentiality we could withhold the data on higher
Multiples. I support giving the information.

Michele Walsh
beeper(b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 12:54 PM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,
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information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From:	Das, Abhik
To:	Frantz, Ivan; Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Wallace, Dennis; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole, W. Kenneth; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); VanMeurs, Krisa
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject:	RE: NEOProm meta analysis of oximetry trials
Date:	Tuesday, October 06, 2009 2:44:13 PM

Out of our 1317 infants we have 4 sets of quadruplets (16 babies) and 15 sets of triplets (45 babies). So we would be excluding 61, or about 5%.

Thanks

Abhik

From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Tuesday, October 06, 2009 2:41 PM
To: Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Wallace, Dennis; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole, W. Kenneth; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: RE: NEOProm meta analysis of oximetry trials

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Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, October 06, 2009 1:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Frantz, Ivan; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: RE: NEOProm meta analysis of oximetry trials

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I think it is very important that we provide the data on twins.
Because of the increasing information on the heritability of both ROP and
BPD, it is important for metanalyses to develop techniques to be able to
Account for this clustering by family unit, unless the babes are independently
Randomized. It is possible that to protect confidentiality we could withhold the data on higher
Multiples. I support giving the information.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 12:54 PM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,
Lisa Askie, who is leading the prospective meta analysis of the oximetry trials for which we are participating from the SUPPORT Trial is asking for birth order and sibling match to be included in the final data set. We do have information on birth order and sibling match in our data; however, there is a question of whether we can share that information due to privacy issues. For example, if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575

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301-496-3790 (FAX)
higginsr@mail.nih.gov

Visit us at www.UHhospitals.org.

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NEOProm meta analysis of oximetry trials
Date: Tuesday, October 06, 2009 2:15:12 PM

I agree with Michelle. Even quads are not that unusual anymore. I don't see why we would view this information differently than other clinical information that's de-identified to the extent feasible (ie, we include birth date only when we need it).

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 12:17 PM
To: Kennedy, Kathleen A; Tyson, Jon E; Smith, Nancy M
Subject: FW: NEOProm meta analysis of oximetry trials
Importance: High

Email is being returned from UT Houston with the following note:

Delivery has failed to these recipients or distribution lists:

Tyson Jon (E-mail)
There's a problem with the recipient's mailbox. Microsoft Exchange will not try to redeliver this message for you. Please try resending this message, or provide the following diagnostic text to your system administrator.

Kennedy, Kathleen A
There's a problem with the recipient's mailbox. Microsoft Exchange will not try to redeliver this message for you. Please try resending this message, or provide the following diagnostic text to your system administrator.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 06, 2009 12:54 PM
To: Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg
Subject: NEOProm meta analysis of oximetry trials

Hi,
Lisa Askie, who is leading the prospective meta analysis of the oximetry trials for which we are

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participating from the SUPPORT Trial is asking for birth order and sibling match to be included in the final data set. We do have information on birth order and sibling match in our data; however, there is a question of whether we can share that information due to privacy issues. For example, if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization).

Please let me know if you are able to share this information on patients in the study of potentially triplets or even higher order multiples for the individual patient meta analysis. If you need to consult your IRB, please do so.

Please send me a response by October 23.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Jody Power
To: Zaterka-Baxter, Kristin
Cc: Michael Cotten; Gloria Siaw; Ronald N Goldberg; Higgins, Rosemary (NIH/NICHD) [E]; Kimberley A Fisher
Subject: RE: eIRB: Notification of Approved Amendment
Date: Tuesday, October 06, 2009 1:51:50 PM

Kris,
I can answer that question. Alamance is a separate legal entity from DUHS and would require its own IRB oversight. That can be accomplished in 1 of 2 ways: (i) by separate contract with their own IRB: or (ii) by contract with Duke to have the DUHS IRB act as their IRB-of-Record for this specific study. For option (ii), I have a template IRB Authorization Agreement to be signed by Duke and the site that establishes the DUHS IRB as the IRB for an external site on a study-by-study basis.

Thank you. Let me know if you need the template to forward to an external site.
Jody

"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

10/06/2009 01:39 PM

To "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Michael Cotten" <cotte010@mc.duke.edu>
cc "Jody Power" <power008@mc.duke.edu>, "Kimberley A Fisher" <kimberley.fisher@duke.edu>, "Gloria Siaw" <gloria.siaw@duke.edu>, "Ronald N Goldberg" <goldb008@mc.duke.edu>
Subject RE: eIRB: Notification of Approved Amendment

Hi Mike,

Would the health system wide approval include Alamance if you decide to recruit there or do they have a totally separate IRB?
Thanks,
Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 06, 2009 1:36 PM
To: 'Michael Cotten'; Zaterka-Baxter, Kristin
Cc: Jody Power; Kimberley A Fisher; Gloria Siaw; Ronald N Goldberg
Subject: RE: eIRB: Notification of Approved Amendment

TERRIFIC!!!!
THANKS for following up!!
Rose

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Tuesday, October 06, 2009 1:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Jody Power; Kimberley A Fisher; Gloria Siaw; Ronald N Goldberg
Subject: Fw: eIRB: Notification of Approved Amendment

HI Rose,

please see below the confirmation of IRB approval of the amendment to allow
us to access charts at DRH for the SUPPORT trial. I met with Jody Power this morning (cc'd on the email), she's the executive director the Duke IRB. She clarified for me that the Duke IRB is health system wide, meaning
that DRH is part of the 'covered entity' and is covered by the Duke IRB Federal Wide Assurance. We still needed DRH internal administrative approval before getting the IRB final approval, as they need to know that
some research is happening there.....(we got that today).....Jody will be
helping to address IRB issues/concerns on the site visit report reply.

thanks
mc

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C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu
----- Forwarded by Michael Cotten/Pediatrics/mc/Duke on 10/06/2009 01:30 PM -----

<eirb@mc.duke.edu>

To: <cotte010@mc.duke.edu>

10/06/2009 01:22 PM

cc:

Subject: eIRB: Notification of Approved Amendment

Please respond to <eirb@mc.duke.edu>

DUHS Institutional Review Board
NOTIFICATION OF APPROVAL

Principal Investigator: Charles Cotten Protocol ID: Pro00015378

Protocol Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Protocol Sponsor(s):

National Institutes of Health

IND#:

IDE#/CMS
Category:

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The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB) has conducted the following activity on the study cited above:

Activity: Amendment

Type of Review: Expedited

Protocol Expiration Date: 4/7/2010

Review Date: 9/30/2009

Pediatric Risk Category: 45CFR46.404 and 21 CFR 50.51 as applicable

Date of Declared Concordance with federally funded grant, if applicable:

DUHS IRB approval encompasses the following specific components of the study cited above:

Protocol version/date:

Consent form reference date: 10/06/2009

Investigator Brochure version/date:

Summary version/date: 09/29/2009

Amendment version/date:

Amendment ID: Amd2_Pro00015378

Federal Funding Agency ID: HD-00-010 Other

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.
No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval of the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five working days of the event.

This study expires at 12 AM on the Expiration Date. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the expiration date.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), FWA 00009025, is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.

Jody Power 10/06/2009

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DUHS IRB Authorized Signature

Final IRB Approval Date

DUMC 2712 * 2424 Erwin Rd * Durham, NC 27705
tel (919) 668-5111 * fax (919) 668-5125

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Michael Cotten"; "Zaterka-Baxter, Kristin"
Cc: "Jody Power"; "Kimberley A Fisher"; "Gloria Siaw"; "Ronald N Goldberg"
Subject: RE: eIRB: Notification of Approved Amendment
Date: Tuesday, October 06, 2009 1:35:00 PM

TERRIFIC!!!!
THANKS for following up!!
Rose

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Tuesday, October 06, 2009 1:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Jody Power; Kimberley A Fisher; Gloria Siaw; Ronald N Goldberg
Subject: Fw: eIRB: Notification of Approved Amendment

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thanks
mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu
----- Forwarded by Michael Cotten/Pediatrics/mc/Duke on 10/06/2009 01:30 PM

<eirb@mc.duke.edu>	
	To
10/06/2009 01:22 PM	<cotte010@mc.duke.edu>
	cc
	Subject
Please respond to	eIRB: Notification of Approved

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

<eirb@mc.duke.edu Amendment
>

DUHS Institutional Review Board
NOTIFICATION OF APPROVAL

Principal Investigator: Charles Cotten Protocol ID: Pro00015378

Protocol Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Protocol Sponsor(s):

National Institutes of Health

IND#: IDE#/CMS
Category:

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB) has conducted the following activity on the study cited above:

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Activity: Amendment Type of Review: Expedited

Protocol Expiration Date: 4/7/2010 Review Date: 9/30/2009

Pediatric Risk Category: 45CFR46.404 and 21 CFR 50.51 as applicable

Date of Declared Concordance with federally funded grant, if applicable:

DUHS IRB approval encompasses the following specific components of the study cited above:

Protocol version/date: Consent form reference date: 10/06/2009

Investigator Brochure version/date: Summary version/date: 09/29/2009

Amendment version/date: Amendment ID: Amd2_Pro00015378

Federal Funding Agency ID: HD-00-010 Other

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.
No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval of the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five working days of the event.

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The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), FWA 00009025, is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and

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Jody Power 10/06/2009

DUHS IRB Authorized Signature Final IRB Approval Date

DUMC 2712 • 2424 Erwin Rd • Durham, NC 27705
tel (919) 668-5111 • fax (919) 668-5125

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From: Susan Hintz
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: Re: SUPPORT o2 sats
Date: Tuesday, October 06, 2009 12:21:22 PM

Thanks Marie. That will help me in my comments.

Susan

Sent from my iPhone

On Oct 6, 2009, at 8:10 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

> It is possible to calculate time with saturations <80% from the
> SUPPORT
> oximetry data, so that should not be an issue.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Tuesday, October 06, 2009 11:08 AM
> To: 'Susan Hintz'; Das, Abhik; Gantz, Marie
> Subject: RE: SUPPORT o2 sats
>
> I think Marie needs to weigh in on this as she has the most experience
> with the oximetry data set.
>
> Rose
>
> -----Original Message-----
> From: Susan Hintz [mailto:srhintz@stanford.edu]
> Sent: Tuesday, October 06, 2009 11:05 AM
> To: adas@rti.org
> Cc: Higgins, Rosemary (NIH/NICHD) [E]
> Subject: SUPPORT o2 sats
>
> Hi Rose and Abhik
>
> I am putting together some comments regarding Hibbs revised sleep
> disordered breathing proposal. As I told Rose, I have really let this
> revised proposal sit unattended because it is really linked to the
> breathing outcomes study, and there is no school age follow-up
> proposal in place yet. However, I will respond to her as I can from
> my point of view.
>
> Anyway, one of the issues is that Hibbs proposes using "% of time
> with o2 sat <80" in the SUPPORT monitoring period as a predictor

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> variable. So, I am assuming that is completely "do-able" from the
> SUPPORT data manipulation point of view? This is a kind of big
> lynchpin to her proposal, and I want to make sure it will be possible
> (relatively easily) - she hypothesizes that greater % of time with O2
> sats<80 in neonatal period (as a maker for "hypoxia") will be
> associated with sleep disordered breathing at extended follow-up.
>
> Thanks
>
> Susan
>
> --
> Susan R. Hintz, M.D., M.S. Epi
> Associate Professor of Pediatrics
> Division of Neonatal and Developmental Medicine
> Stanford University School of Medicine
> 750 Welch Road, Suite 315
> Palo Alto, CA 94304
> ph: 650-723-5711
> fax: 650-725-8351

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From: Cunningham, Meg
To: nfiner@ucsd.edu
Cc: fmartinez@ucsd.edu; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: SUPPORT Call
Date: Tuesday, October 06, 2009 11:46:04 AM

Hi Dr. Finer,

Do you have an agenda or any materials to distribute before the call tomorrow? If so, please send them to me so I can distribute.

Thanks,
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org

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From: Zaterka-Baxter, Kristin
To: Michael Cotten; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Phelps, Dale; Ronald N Goldberg; Kimberley A Fisher; Auman, Jeanette O.; Gantz, Marie
Subject: RE: case question
Date: Monday, October 05, 2009 1:20:37 PM

Hi,

I've checked with Jenny and Marie as well and this scenario will not cause and edit or query programmatically or statistically. The SUPP10 exam date is after the NG03 discharge date.

Thanks,
Kris

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Monday, October 05, 2009 12:58 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Phelps, Dale'; Ronald N Goldberg; Kimberley A Fisher; Zaterka-Baxter, Kristin
Subject: RE: case question

HI Rose and Dale,

another query....we have an exam that found 'plus' disease a couple of weeks after discharge to home. The current NGO3 outcome page for patient 73171 ROP says 'no plus disease'...but the SUPP10 will include it, as it was diagnosed after discharge at an outpatient exam. (This eventually regressed.)...my question is that I am anticipating a query as gdb outcome will disagree w/ SUPP10 outcome....(plus disease in SUPP, no plus disease at status in GDB).....will this be a data consistency problem?

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
10/05/2009 09:11 AM

To: "'Phelps, Dale'" <Dale_Phelps@URMC.Rochester.edu>, Michael Cotten <cotte010@mc.duke.edu>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>

cc: Kimberley A Fisher <kimberley.fisher@duke.edu>, Ronald N Goldberg <goldb008@mc.duke.edu>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>

Subject: RE: case question

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I agree with Dale - try to find the ROP exam where the child was fully vascularized based on DC summary. I checked the GDB manual - it appears that this is "Undetermined" based on the following of ROP in ZONE II:
3= Undetermined ROP status in either eye (and neither had 'severe ROP")
EITHER eye met one of the following criteria:
* Immature vessels in zone I or zone II
* Immature vessels reaching zone III for only 1 consecutive examination
* Stage 1 or 2 ROP in zone III for only 1 consecutive examination
* Stage 3 ROP in zone III
* ROP in zone I or zone II
* plus disease

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, October 04, 2009 1:07 PM
To: Michael Cotten; Zaterka-Baxter, Kristin
Cc: Kimberley A Fisher; Ronald N Goldberg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: case question

Hi Mike,

I agree with your interpretation.

For SUPPORT, this infant's official primary outcome criteria are not met. There are not two sequential examinations improving in zone III. (not even one)
It is a missing primary outcome.

The adjudication process of such cases may be able to assign a "probably favorable outcome" to this infant as a secondary outcome, but I'm not confident of that. We will not be able to complete that before the abstract submission.

What puzzles me is why an ophthalmologist would not do a follow up examination on a very sick baby with zone II stage 2 ROP, even though now regressing. This was probably not a stable baby (he died in first year). His ROP had gone from stage 1 to stage 2 on the last two eye examinations, even though the last examination showed signs of regression. It was only one examination. Statistically, it is unlikely that he progressed to threshold after 43 weeks, but not unheard of.
:-(

One puzzle: why did the discharge summary say 'fully vascularized'? Was there another examination that you've missed in the medical record? One way to 'easily' skim for this would be in the medication record, if you have one electronically recorded. Look for orders for the dilating drops for an eye examination. It is a good sign of a probable examination.

Dale

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Sunday, October 04, 2009 8:41 AM
To: Zaterka-Baxter, Kristin; Phelps, Dale
Cc: Kimberley A Fisher; Ronald N Goldberg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: case question

Hi Kris and Dale...my review of primary ROP outcome for case 72501 generates a question:

this baby's last exam was at 45 weeks post menstrual age. THe exam results clearly state zone 2 stage 2 OU,,,but also cleary written by the ophthalmologist as 'regressing.' Also,,,at the bottom of the note where the ophthalmologist write the recommended follow up, the opthalmologist

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wrote
"1 year".....The previous exam, at 43 weeks PMA was zone 2 stage 1 OU. This was the baby's last exam prior to the baby's death at about one year of chronologic age, about 4 months before his first scheduled outpatient eye exam. The NICU discharge summary says "fully vascularized"....but I'd go with the ophthalmologist's exam note as primary source.

per the ngo3 in gdb definition for 'favorable' rop outcome at status, the def includes "rop in zone II or III, but determined to be clearly regressing" (which I think this baby meets)....For SUPPORT in the Manual of Ops,,,this isn't a defintion of 'favorable'....the SUPPORT MOP says "favorable" is an exam w/ full maturation at all clock hours or two sequential exams to zone III...

my take on this is that on GDB NGO3 we code "favorable", but the SUPP10 should list the baby as: Final outcome lost to follow up at 55 weeks "YES",,,,and Final ROP outcome determined at 18 month followup "NO"..because we lack an exam between 43 weeks post menstrual age and 55 weeks that had full vascularization or two sequential w/ vessels in zone III...

is this a correct interpretation?

C. Michael Cotten MD MHS
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From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Error message when entering SUPPORT data
Date: Monday, October 05, 2009 12:02:18 PM

(b) (6) [redacted]

Jenny

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 05, 2009 12:01 PM
To: Auman, Jeanette O.
Subject: RE: Error message when entering SUPPORT data

Good to have you back. (b) (6) [redacted]
Take care
Rose

-----Original Message-----
From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Monday, October 05, 2009 11:59 AM
To: ssayers@pedsmail.ucsd.edu; wrich@ucsd.edu
Cc: Pickett, James; Auman, Jeanette O.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Error message when entering SUPPORT data

Hello,

Can you tell us which particular response(s) on the NG07 you changed when you received this error?

Thank you,
Jenny

Jeanette Auman
Research Programmer/Analyst
RTI International
(919) 237-1213
joa@rti.org

----- Original Message -----
From: Sayers, Suzanne A <ssayers@pedsmail.ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Fri Oct 02 17:53:49 2009
Subject: Error message when entering SUPPORT data

Good afternoon Rosemary,

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I am trying to resolve the latest "batch" of SUPPORT BPD queries that were sent to Wade Rich and I keep getting the following programming error message when I try to correct and complete the NG07:

MCH_IsMissingCode has been called on a value that is not a String Type (Field 2).

I have never encountered this error code and any advice would be greatly appreciate. Thanks for your attention to this matter in advance.

Best Regards,

S. Alex Sayers
Data Coordinator - Neonatology
402 Dickinson Street, Suite 1-140
San Diego, CA 92103-8774
Mail Code 8774
P: 619-543-5854
F:619-543-3812

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From:	Susan Hintz
To:	srhintz@stanford.edu
Cc:	Maureen Hack; Jane Hammond; Higgins, Rosemary (NIH/NICHD) [E]; betty vohr; M Bethany Ball; Gerry Taylor; Ken Poole; adas@rti.org; Seetha Shankaran; Neil Finer; Krisa Van Meurs; dstevenson@stanford.edu
Subject:	SUPPORT Neuroimaging Cohort Extended Follow-Up Subcommittee Update
Date:	Monday, October 05, 2009 12:00:10 AM
Attachments:	FINAL_SchoolAgeFollowUpSUPPORTNeuroimaging.pdf FINAL_Grid_SUPPORTSchoolAge_visit.pdf

Dear SUPPORT Neuroimaging Cohort Extended Follow-Up Subcommittee:

Thank you for your continued work and help on this long-term project! This email will serve as a brief quarterly update of our study.

SUPPORT Neuroimaging Cohort Extended Follow-up Protocol

o Subsequent to the recommendations of our subcommittee, final discussion of the SUPPORT Extended Follow-up protocol took place at the Neonatal Research Network Steering Committee meeting in June 2009.

o The steering committee approved the recommended changes, which included moving follow-up window forward by 6 months to 6 1/2 to 7 1/2 years, and the final changes to the test/questionnaire grid.

o The protocol is now final and is attached. The visit battery grid is also attached.

Tracking for school-age follow-up

o 18-22 month follow-up is ongoing, with greater than 90% follow-up rate so far.

o SUPPORT Extended Follow-up status form for documenting contact with patient families at 3-4 years **is required for each child**.

o Successful completion of this status form is required for release of capitation funds from NICHD to Network site - so this is a powerful incentive for successful tracking contacts.

Manual and forms development

o The most up-to-date versions of all tests and questionnaires to be used in the school-age follow-up visit have ordered (or are being ordered) by RTI, with the help of Jane Hammond and Jamie Newman. Manual and forms development is our next important step.

o The 6 1/2 to 7 1/2 year window for the first enrolled child will open in November 2011 - but only 10 children have windows opening before September 2012.

o Therefore, training will be targeted for late fall 2011 (catching the early patients later in their windows).

o **Our plan is to have manual and forms ready by late fall or early winter 2010 - giving Network sites about a year to provide final feedback and get through their IRB's before school age follow-up visits begin.**

Neuroimaging update

o Neuroimaging cohort size: 548 patients with "complete" neuroimaging (per MRI

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Master FU spreadsheet). **This cohort is even larger than we had anticipated or hoped for. It will certainly be the largest extremely preterm cohort worldwide with comprehensive neonatal neuroimaging including MRI and planned school age follow-up.**

o Cranial US readings: Central readings by two central readers (Dorothy Bulas, Tom Slovis) are nearly complete - final CUS readings will likely be done by end October. Data are being entered as central reader forms are completed. **The plan is for preliminary analysis of CUS findings in time for PAS Late Breaker deadline (end February).**

o MRI readings: Whole Body Hypothermia for HIE trial MRI readings are now complete (and analysis in progress) - therefore, SUPPORT MRI central readings have been back on track and are currently ongoing. These readings are complex and time intensive. The goal was originally for completion of readings in time to allow preliminary analysis for PAS Late Breaker - but this may not be possible. However, preliminary analysis may be ready by the time of the PAS meeting itself, and could potentially be presented in part at the State of the Art Symposium on Neuroimaging in Preterm infants (organized by Mike O'Shea and Laura Ment).

Also, as you are aware, the SUPPORT main trial (Neil Finer, et. al.) enrollment was completed in February 2009. Analyses of primary short-term outcomes of this extremely important trial (including BPD and ROP) are underway.

Thank you again for your ongoing help and support. I will definitely be contacting you for further help and guidance as we embark on manual and forms development.
Susan

--

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Extended Follow-up at School Age (6½ to 7½ years) for the SUPPORT Neuroimaging and Neurodevelopmental Outcomes Cohort

Subcommittee:

Susan Hintz, M.D., M.S. Epi.
Betty Vohr, M.D.
Maureen Hack, M.D.
H. Gerry Taylor, Ph.D.
W. Kenneth Poole, Ph. D.
Jane Hammond, Ph.D.
Abhik Das, Ph.D.
Seetha Shankaran, M.D.
Neil Finer, M.D.
M. Bethany Ball
Rosemary Higgins, M.D.

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I) INTRODUCTION:

The **Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)** is a prospective, randomized, factorial 2x2 design multi-center trial conducted by the NICHD Neonatal Research Network (enrollment completed February 2009). The trial will evaluate if CPAP and a permissive ventilation strategy and lower SpO_2 targets (85-89% vs. 91-95%) will result in increased survival without bronchopulmonary dysplasia (BPD) and increased survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. **The SUPPORT Neuroimaging and Neurodevelopmental Outcomes Study** is a prospective secondary study to SUPPORT of cranial ultrasound (CUS) at 4-14 days ("early CUS") and 35-42 weeks postmenstrual age (PMA) ("late CUS"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT. The study was launched in May 2005, and 16 NICHD NRN sites participated. This study will allow us to assess the comparative and combined capabilities of early and late CUS and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age. The SUPPORT Neuroimaging and Neurodevelopmental Outcome cohort will be the largest such cohort assembled to date.

Children born extremely prematurely continue to have significant neurodevelopmental challenges in later childhood, yet many subtle but significant cognitive and performance problems cannot be delineated until school age. Early and accurate prediction of neurodevelopmental outcome would be invaluable, but CUS and other early variables do not reliably predict outcomes. White matter (WM) injury has been strongly implicated in neuromotor and cognitive impairment, and a link between WM injury and gray matter developmental disruption appears to exist. MRI is better than CUS in identifying subtle and diffuse WM injury, as well as cerebellar and gray matter abnormalities. Previous studies of preterm infants have shown WM injury by MRI to be significantly associated with CP and adverse *neurosensory* outcome, independent of CUS abnormalities. An independent association with *cognitive* impairment in early childhood has not yet been demonstrated. However, subtle neonatal MRI abnormalities may predict cognitive problems in early school age that cannot yet be delineated at 18-24 months. In addition, higher rates of behavioral and executive function impairments in childhood have been reported among very preterm infants, and previous studies have suggested that WM injury seen on neonatal MRI may predict these impairments. **We therefore propose to follow the SUPPORT Neuroimaging cohort at 6½ - 7½ years to test the primary hypothesis that neonatal brain MRI is superior to neonatal CUS in predicting death after discharge or cognitive impairment (Wechsler Intelligence Scale for Children-IV (WISC-IV) IQ<70) at school age.** We will also test whether neonatal brain MRI is superior to CUS in predicting neuromotor impairment, disability, and less severe cognitive impairment. We will also assess whether injury severity on neonatal MRI is associated with longitudinal cognitive and disability level changes, examine cognitive impairment and disability between ventilatory and oxygenation saturation SUPPORT intervention groups, and determine whether neonatal MRI is superior to CUS in predicting adverse executive and behavioral outcomes.

The SUPPORT Neuroimaging cohort is valuable and unique among other preterm cohorts worldwide. By pursuing 6½ - 7½ year follow-up, the NICHD NRN is in an outstanding position to substantially contribute to our understanding of later extremely preterm outcomes and their prediction.

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II) HYPOTHESES:

Among children enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary with complete neuroimaging and surviving to hospital discharge:

PRIMARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment (WISC-IV IQ<70) at 6½ - 7½ years.

SECONDARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment (WISC-IV IQ<70) at 6½ - 7½ years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or disability, or disability among survivors, at 6½ - 7½ years.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the risks of cognitive impairment, disability, or neuromotor impairment including CP between ventilatory or oxygenation saturation SUPPORT intervention groups in this sub-cohort.
- Neonatal brain MRI will be superior to neonatal CUS in predicting mild cognitive impairment (WISC-IV IQ 1-2 SD below population mean) at 6½ - 7½ years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting CP and neuromotor/movement impairment at 6½ - 7½ years.
- Moderate to severe white matter injury on neonatal neuroimaging will be associated with behavior and executive function impairments at 6½ - 7½ years.
    - Neonatal brain MRI will be superior to neonatal CUS in predicting behavioral and executive function impairments at 6½ - 7½ years.
- Severe developmental impairment and severe cerebral palsy at 18-22 months will be highly predictive of severe disability at school age, but mild or moderate impairment at 18-22 months will be poorly predictive of later outcome group.
- Injury severity and pattern on neonatal MRI will be associated with longitudinal cognitive and disability level changes (18-22 months corrected age → 6½ - 7½ years).
- Brain injury pattern and topography on neonatal MRI will be associated with anatomic and functional type of CP at school age.
- High rates of health-related quality of life challenges and chronic or disabling conditions will be observed.
    - These findings will be associated with moderate-severe brain injury on neonatal neuroimaging.
- Local readings of neonatal MRI will be less predictive of 6½ - 7½ year outcomes than central reading.

Specific Aims:

- To assess cognitive, neuromotor, functional and behavioral outcomes of the SUPPORT Neuroimaging cohort at 6½ - 7½ years of age
- To examine the independent associations of neonatal neuroimaging findings with neurodevelopmental outcomes
    - Assess the absolute and relative value of early and late neonatal CUS and neonatal MRI, alone and in combination with other risk factors, to predict normal and impaired outcomes

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- To examine longitudinal changes in cognitive and overall impairment level from 18-22 month to 6½ - 7½ year exams, and assess relationship of neonatal neuroimaging abnormalities and other variables.
- To compare 6½ - 7½ year neurodevelopmental outcomes of ventilation and oxygenation SUPPORT randomized groups in this sub-cohort.

II) BACKGROUND AND SIGNIFICANCE:

Long-term neurodevelopmental outcomes of extremely preterm infants:

Despite advances in perinatal and neonatal management and improvement in survival, short-term neurodevelopmental outcomes of extremely preterm and extremely low birth weight (ELBW) infants remain guarded (Vohr, Hintz #1, Hintz #2, Costeloe). This high frequency of disability in very early childhood (18-24 months) makes longer-term neurodevelopmental outcome studies crucial. Evaluation at a later age allows identification and delineation of a broader range of problems, including cognitive delay, more subtle motor, movement, and coordination disabilities, and behavioral and executive function problems to be determined. It also allows for assessment of the strength of perinatal and neonatal variables as potential predictors of long-term outcomes, and for longitudinal analysis to determine the predictive value of early disability.

Later childhood follow-up studies have demonstrated that significant neurodevelopmental and cognitive impairment continue for extremely preterm infants. In the 206 ELBW infants followed at 5 years in the Finnish National Cohort (Mikkola), 20% had major disabilities, and 19% of those <27 weeks were diagnosed with cerebral palsy (CP). The EPICure Study Group (Marlow) reported on 241 <26 week survivors at 6 years; severe overall cognitive delay was present in 21% compared with test norms (41% compared with term controls), and disabling CP was diagnosed in 13%. In a study of 219 ELBW infants at 8 years (Hack #1), Hack, et. al. reported CP in 14%, severe cognitive impairment in 15%, moderate-severe cognitive impairment in 38%, and significant motor skills problems in 27%. Families reported substantial functional limitations, including emotional delay, trouble understanding or communicating, and need for medication or equipment. Needs for special services were significantly greater than for the normal birth weight (NBW) control group. Impairment in academic (32%) and adaptive skills (48%) have also been reported among ELBW children, and are significantly more frequent than in NBW controls (Taylor). In an ELBW or <28 week EGA cohort at 8 years (n=275), Anderson, et. al. reported significant impairment across all tested cognitive and educational abilities compared with NBW controls (Anderson #1). Although improvements in neurosensory impairment rates have reported over time with successive ELBW birth cohorts in VICS since the 1970's, neurologic disabilities continue to be substantially more common among ELBW children at school age than their normal birth weight peers (Doyle #1).

Summary: Children born extremely preterm or ELBW continue to have significant motor and cognitive disabilities in childhood, as well as more subtle functional and adaptive impairments. Delineation of some of these problems may not even be reasonably undertaken until 5-8 years of age. The true impact of these impairments may not be felt until later school age (Saigal).

Neonatal CUS and other variables to predict neurodevelopmental outcomes

CUS and short-term outcomes (18-24 months)

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The association of severe neonatal CUS abnormalities and adverse short-term neurodevelopmental outcome has been reported in numerous studies (Vohr, Hack #2). But the strength of this association appears to be consistent primarily for combined developmental and neuromotor endpoints, or for CP or motor disability alone, but not for pure cognitive delay (deVries, Hack #2, Wood). In addition, severe CUS abnormalities are not uniformly predictive of adverse short-term outcome and normal CUS do not predict normal outcome in this high-risk population (deVries, Hack#2, Laptook, Ancel, Pinto-Martin). In fact, in a predictive modeling analysis, Ambalavanan found that severe grade of IVH explained only 8% of the variance in low MDI and 5% of the variance for major handicap at 18-22 months (Ambalavanan).

CUS and long-term outcome (5-8 years)

Reported associations of neonatal CUS findings and long-term outcomes are inconsistent. Sherlock, et. al. (Sherlock) reported that neurodevelopmental impairment at 8 years varied little with increasing severity of IVH; a trend for worse cognitive and neurosensory outcome with higher grade IVH in that study was explained solely by the outcomes of the small number of patients with parenchymal hemorrhage. The Neonatal Brain Hemorrhage Study (NBHS) showed that 88% of LBW patients with germinal matrix or IVH had normal cognitive outcomes (Whitaker) at 6 years.

Nevertheless, several analyses have reported abnormal neonatal CUS to be "significantly associated with" adverse long-term neurodevelopmental outcomes in ELBW cohorts. For instance, Mikkola found an association of abnormal CUS with CP and IQ at 5 years (Mikkola), and Taylor found an association of abnormal CUS with executive function and memory on the NEPSY (Taylor). However, the definition of CUS "abnormality" varies among studies, with some analyses including markers of white matter injury (PVL or ventricular enlargement (VE)) and others limiting only to IVH. In addition, a finding of association does not specifically address the independent *predictive* power of neonatal CUS, particularly with respect to cognitive outcome in later childhood. In fact, Hack, et. al. demonstrated that only 36% of those with a Mental Processing Composite (MPC) of <85 at 8 years had had an abnormal CUS, and only 45% of those with MPC<70 (Hack #3). In the 6-year follow-up of the NBHS cohort, only 12% of those with GM/IVH had borderline IQ or mental retardation (Whitaker). In that study, PVL/VE was separately assessed; this revealed a stronger 56.5% of those with PVL/VE had borderline IQ or mental retardation. This may be a clinical insight to the importance of white matter (WM) injury for longer-term adverse outcomes *including cognitive outcomes*. Nevertheless, more that 40% of patients with PVL/VE had normal intelligence at 6 years - a finding, which, in turn, may serve to underscore the inability of routine CUS to see anything more subtle than the most definitive WM injury.

Other potential predictors of long-term neurodevelopmental outcome:

Investigators have attempted to determine other, more reliable predictors of longer-term outcomes of preterm infants. Doyle reported on prediction of survival free of major disability at 5 years among the surviving VICS cohort on the basis of the *number of adverse neonatal variables* experienced by the child (Doyle #2). Although observed and predicted values were similar, the outcome was not specifically focused (i.e., combined neurologic/neurosensory/cognitive endpoint), the observed 95% CI range was broad for 2 and 3 variable groups, and the patient numbers were quite small. Others have assessed the predictive value of *earlier neurodevelopmental findings*. Marlow found that only severe

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disability at 30 months was highly predictive of 6-year outcome; 38% of children defined as mild or moderately disabled and 24% with "no disabilities" had moderate or severe disabilities at 6 years. Hack (#3) found the positive predictive value of MDI<70 at 20 months for MPC<70 at 8 years to be extremely poor (PPV=0.37). However, some intriguing links between neonatal brain injury and longitudinal decline in cognitive ability have been reported. In follow-up to the I-IVHP trial, Ment found that cognitive scores declined from 36 to 96 months only in the subset of patients with early IVH coupled with PVL or VE (Ment). Also from the I-IVHP trial, the presence of spastic cerebral palsy at 3 years was more strongly predictive of IQ<70 at 8 years than was cognitive testing at 3 years (Pleacher). These findings are interesting, but perhaps not surprising, in light of the proposed mechanism linking white matter injury with reduced connectivity, gray matter loss, and cognitive delay (Boardman, Inder).

Summary: Aggregate abnormal findings on neonatal CUS do not reliably predict either short- or long-term neurodevelopmental outcomes, although markers of WM injury appear to be stronger links. Early cognitive measures also do not predict later cognitive outcome well in most circumstances. These findings emphasize the deficits of routine CUS to detect subtle injury, and also underscore the poor predictive validity of early cognitive measures for later cognitive outcomes (Aylward). These findings also suggest that better delineation of neonatal WM injury may enhance efforts to predict outcomes.

MRI: Delineation of injury and predicting outcomes

Imaging brain injury:

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Studies comparing the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period have shown that MRI detects white matter injury better than CUS (Maaloof, Childs), and provides additional information on brain development not noted by cranial US. Studies have also demonstrated that subtle and diffuse WM injury, not detectable by CUS, may be common among preterm infants at term (Counsell).

White matter injury and cognitive outcome:

Cognitive delay is a significant impairment and difficult to predict. Recent studies have demonstrated that WM injury in the preterm infant is associated with both reduced cortical gray matter volume, and with reduced deep gray matter volume by MRI at term equivalent age (Inder, Boardman). There are several potential mechanistic pathways, including via direct axonal or subplate neuron injury that may explain this finding. The common endpoint is reduced connectivity, limited neuronal differentiation, and poor cognitive outcome. In fact, recent research using MRI tractography in a series of former preterm infants at approximately 2 years of age has provided at least proof of concept for this theory of reduced cortical and thalamic connections after WM injury (#2 Counsell).

Brain and WM injury by MRI and executive and behavioral outcomes in preterm infants:

Extremely low birth weight and very preterm infants have been reported to be at greater risk for executive dysfunction, as well as emotional and behavioral problems at 2 years, 4 years and at school age (#2 Anderson, Woodward #1, Taylor). These problems are infrequently the focus of neurodevelopmental outcomes studies, and are considered by some to be less serious than cognitive impairment. However, impairments across these domains have substantial impact on academic achievement, follow-up needs, and family

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interactions. Recent studies have suggested that these impairments may be associated with specific brain injury types and patterns among preterm children. In a brain diffusion tensor imaging (DTI) MRI study of preterm and term adolescents, Skranes, et. al. (Skranes) demonstrated that the preterm group were more likely to have attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) diagnoses or symptoms. Those with ADHD and ASD had lower fractional anisotropy (FA) in many WM areas, consistent with WM injury and impaired WM connectivity throughout the brain. Recent analyses have also demonstrated that WM injury on near-term MRI may predict executive and behavioral problems among preterm infant in early childhood. In a single center study, abnormal near-term MRI in VLBW infants was associated with positive M-CHAT screen in early childhood (Limperopoulos). Impaired working memory performance (Woodward #2) and self-regulation (Clark) at 2 years have both been associated with moderate-severe WM injury on near-term MRI. Specific regional injury patterns have furthermore been associated with working memory deficits.

MRI in preterm infants and early neurodevelopmental outcome

After early studies suggesting that MRI at near term was a more powerful predictive tool than CUS for short-term neurodevelopmental outcome (Valkama, Roelents-van-Rijn, Mirmiran), larger MRI studies were undertaken. Many have been single-center efforts, focused chiefly on the association of early neurodevelopmental outcomes with MRI findings in preterm infants at term and earlier, and without extensive comparison of the predictive validity of MRI and CUS. Among these, Miller, et. al. (UCSF, <34 weeks EGA, 86 survivors) and Dyet, et. al. (Hammersmith, <30 weeks EGA, 119 survivors) described MRI findings from birth through near-term and found that WM injury, particularly diffuse injury, was common and was associated with adverse neurodevelopmental outcomes. Recent evidence has also suggested that WM injury on neonatal MRI predicted motor developmental delays at 1 year corrected age with high specificity among very preterm infants (Spittle). Cerebellar injury, not easily seen with routine CUS, was also a prognostic indicator of poor outcome. Of importance, although MRI data were meticulously obtained, only 66% of the group had complete follow-up information.

However, other groups have preterm MRI cohorts, with research aims that include comparison of predictive capabilities of MRI and CUS.

- The 2-year neurodevelopmental outcomes of the New Zealand (NZ) cohort (Woodward #3) (<30 weeks EGA, 167 survivors) revealed that 1) presence of moderate-severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) although increasing severity of WM injury was associated with worse Bayley MDI scores, an independent association of moderate-severe WM injury with severe cognitive delay was not reached. Although sensitivity of moderate-severe WM to predict CP (65%), neurosensory impairment (82%) and severe cognitive delay (41%) was improved over abnormalities on CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n=29) or severe (n=6) WM injury was small, and approximately half of those did not have neurodevelopmental impairment.
- The 2-year results of the Australian cohort (<1250 g or <30 weeks EGA, n=221) (Hunt) showed "major" white matter injury to be a more significant independent risk factor than PVL for CP. Major WM injury was found to be an independent risk factor for

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neurosensory disability where PVL was not. IVH grade 4 was not found to be a significant risk factor for either outcome.

- **SUPPORT Neuroimaging and Neurodevelopmental Outcomes cohort:** The birth date of the first enrolled patient was 5/10/05. Enrollment was completed with SUPPORT main trial in February 2009, and follow-up at 18-22 months is ongoing.

SUPPORT Neuroimaging cohort: Unique and valuable

The SUPPORT Neuroimaging cohort, comprised of ~530 extremely preterm infants surviving to near-term with complete CUS and MRI neuroimaging will be the largest preterm brain MRI cohort worldwide with comprehensive early childhood follow-up. This cohort is also a higher-risk group than other cohorts, and thus targets one of the most important outcomes groups. The SUPPORT Neuroimaging cohort is inherently exceptional due to its development within a randomized controlled trial. Thus, the management profile of a crucial neonatal care component has been more carefully controlled and monitored than would otherwise be the case. This also allows for secondary analyses of the association of respiratory management strategies with subtle MRI findings and with outcomes. The SUPPORT Neuroimaging cohort also has a number of advantages over other preterm/MRI cohorts:

1) New Zealand (NZ) cohort:
    a. Setting: SUPPORT: Embedded in a randomized controlled trial within a multicenter network with focused neurodevelopmental follow-up priorities; NZ: two centers one in New Zealand another in Melbourne, Australia, with a primary focus on MRI imaging
    b. EGA/risk profile:
        i. SUPPORT: <28 weeks EGA; NZ cohort: <30 weeks. In the NZ cohort, only 87/167 were <1000 g BW, and 95/167 were <28 weeks.
    c. Cohort size: SUPPORT: ~530 survivors to near-term; NZ: 167 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. SUPPORT: Two CUS required by the study protocol at specific times (4-14 days and near-term); NZ: number and timing of CUS not required as part of study protocol, but reported CUS usually obtained within 2 days, 5-7 days, 4-6 weeks; if "abnormality" detected, more frequently performed.
        ii. SUPPORT: central reader, detailed data collection; NZ: No central reader. "Worst" CUS findings recorded only related respect to PVL/echolucency, grade 3 or 4 IVH
    e. Timing/interpretation of MRI:
        i. BOTH: Near-term
        ii. BOTH: Central reader
        iii. SUPPORT: detailed MRI central reader data collection form; NZ: central reader data collection instrument not known, but MRI abnormality categories broad.
    f. Non-imaging data collection:
        i. SUPPORT: extensive, including detailed respiratory data; NZ: less detailed
2) Australia cohort:
    a. Setting: Single center in Melbourne, Australia

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b. EGA/risk profile:
    i. <30 weeks, <1250 g.
c. Cohort size: 221 survivors at 2 years.
d. Timing/interpretation of CUS:
    i. Not required, retrospectively gathered data (communication, Rod Hunt).
    ii. "Worst" CUS findings gathered - PVL, grade 4 IVH
e. Timing/interpretation of MRI:
    i. Near-term
    ii. Central reader
f. Non-imaging data collection:
    i. Routine

3) Hammersmith cohort:
    a. Setting: Single center
    b. EGA/risk profile:
        i. <30 weeks.
    c. Cohort size: 119 survivors at 2 years. **Note: complete follow-up data were available for only 66% of the group**
    d. Timing/interpretation of CUS:
        i. CUS not focus – studies thus far report MRI
    e. Timing/interpretation of MRI:
        i. MRI serial – from birth to near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
4) UCSF:
    a. Small, single center
    b. <34 weeks
    c. 86 survivors at 2 years
    d. CUS not focus – MRI's serial from birth to near-term
    e. Non-imaging data routine

Summary: MRI is better than CUS in identifying subtle and diffuse white matter injury, which is relatively common among preterm infants at term, as well as cerebellar, and gray matter abnormalities. Early small and single-center studies suggested that MRI better predicts adverse neuromotor outcome than CUS. Two-year results of the NZ cohort have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities, but not with adverse cognitive outcome. The extent to which these findings will be enhanced and clarified, and how or when MRI should be applied in routine clinical practice, awaits the 18-22 month follow-up results of the larger, higher-risk SUPPORT Neuroimaging cohort. However, a biologic mechanism exists for the link between WM injury and cognitive impairment. Early neurodevelopmental findings are poor predictors of later challenges, but subtle neonatal WM abnormalities by MRI may predict cognitive, behavioral, and executive function impairments at school-age that cannot be delineated at 18-22 months.

Later outcomes: Need for SUPPORT Neuroimaging extended follow-up

Evidence for altered brain development: Corroboration of need for long-term follow-up

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Short-term neurodevelopmental outcomes are only a tiny window into the future of a former preterm child. Difficulties in cognition, performance, verbal/language skills, attention and behavior may not be delineated until later ages. There are also data to support the concept that even minor, undiagnosed brain injury sustained preterm infant is associated with disordered brain development. Rademaker, et. al. found that even minor differences in lesion severity on MRI performed at 8 years of age in <32 week EGA appeared more accurate in prediction of IQ and total impairment score than neonatal CUS (Rademaker). These findings may suggest that subtle injury could have been seen on *neonatal* MRI, which in turn, could have aided in prediction. In a DTI and volumetric MRI study, Yung demonstrated that *neurologically normal* LBW preterm infants at 8-12 years had significantly reduced WM volumes than term controls, and that this was significantly related to reduced IQ (Yung). This finding again suggests that early WM injury leading to reduced volume may have been identifiable on neonatal MRI. Kesler, et. al. described high-resolution MRI results from 73 preterm and 33 term infants at 7-11 years of age; preterm infants had disorganized cortical development, potentially involving disrupted neural migration (Kesler).

Importance of SUPPORT Neuroimaging secondary long-term follow-up

- Our current ability to predict later childhood outcomes from perinatal and neonatal variables is limited. The prognostic validity of neonatal CUS findings is limited, particularly for cognitive outcomes. Even early childhood neurodevelopmental outcome, apart from severe impairment, do not accurately predict later childhood neurocognitive outcome. MRI holds promise as a better predictive modality, but neonatal MRI has not been evaluated on a large scale with respect to long-term, school-age outcomes.
- Performance skills are different at 18-22 months than 6½ - 7½ years. Assessments at the later age may uncover subtle, yet significant problems, including attention/behavior problems, language and verbal delays, and academic impairment, which may be predicted by neonatal WM brain injury seen by MRI.
- The SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary was designed with MRI/CUS predictive comparison in mind.
- 18-22 month follow-up is already part of this secondary study. Thus, there is a crucial and rare opportunity to evaluate longitudinal neurodevelopmental changes, and importantly, how neonatal brain injury patterns and other variables may be associated with changes in cognitive or functional outcomes over time.
- This is a prospectively enrolled secondary cohort, embedded within SUPPORT RCT. These patients have therefore had a more consistent respiratory management approach, and comprehensive respiratory data collection. This provides a unique opportunity for analyses of randomized ventilation/oxygenation arms of Neuroimaging cohort outcomes at 6½ - 7½ years.
- Neurodevelopmental follow-up is already a focused objective of the NICHD NRN, and extended 6-7 year follow-up has recently been undertaken for a previous trial (Shankaran). In developing this SUPPORT Neuroimaging school-age follow-up protocol, we have been able to utilize experience gained from the challenges faced during the previous extended follow-up project.
- Other preterm/MRI cohorts, notably the NZ cohort, already have moved forward with longer-term follow-up (Clark, Woodward #1).

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III) STUDY DESIGN:

Objective: This is a prospective, extended follow-up study of 6½ - 7½ year neurodevelopmental outcomes of the SUPPORT Neuroimaging Secondary cohort. We will evaluate and compare the capabilities of *neonatal neuroimaging* - CUS and near-term MRI – to predict cognitive impairment, disability, and neuromotor impairment at 6½ - 7½ years. We will evaluate longitudinal changes in neurodevelopmental outcome, and assess associated neuroimaging findings and other variables. We will also determine if ventilatory or oxygenation saturation SUPPORT interventions are associated with differences in 6½ - 7½ year neurodevelopmental outcomes.

Outcomes:

- Primary:
  - IQ by WISC-IV<70 or death after discharge
- Secondary:
  - IQ score (continuous) by WISC-IV among survivors
  - Disability
    - Severe: Any of: WISC-IV>3 SD below mean, severely impaired neuromotor/functional outcome (non-ambulatory, GMFCS level 4-5), profound hearing loss or blindness (not functionally correctable),
    - Moderate: Any of: WISC-IV2-3 SD below mean, moderately impaired neuromotor/functional outcome
    - Mild: Any of: WISC-IV1-2 SD below mean, mildly impaired neuromotor/functional outcome (abnormal neurologic exam, but walking independently, GMFCS level 1-2)
  - Neuromotor, movement
    - Cerebral palsy, classified anatomically and functionally according to Definition and Classification of Cerebral Palsy, February 2007 guidelines (Baxter) ; Motor and coordination impairment, as determined by administration of the Movement Assessment Battery for Children, version 2 (M-ABC-2) (Burns, Smits-Engelsman).
  - Mild-moderate cognitive impairment (WISC-IV 1-2 SD below mean), severe cognitive impairment (WISC-IV 2-3 SD below mean), and profound cognitive impairment (WISC-IV>3 SD below mean)
  - Executive function and achievement delays (evaluated by NEPSY-II subtests; Behavior Rating Inventory of Executive Function (BRIEF, parent form) (Roze); Woodcock-Johnson III subtests (Taylor))
  - Behavioral and attention deficits (evaluated by Strengths and Difficulties Questionnaire (SDQ) (Goodman, Muris); Conners' Rating Scale (ADHD short form only); Social Communication Questionnaire (SCQ) (Chandler, Eaves))
  - Chronic conditions and health-related quality of life concerns (evaluated by the Questionnaire for Identifying Children with Chronic Conditions – revised (QUICCC-R) (Stein); the Pediatric Quality of Life Inventory (Peds QL) (Majnemer))

Study population:

- The study population (SUPPORT Neuroimaging cohort) will be comprised of the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary enrollees

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who survived to discharge, with complete neuroimaging. **It is estimated that approximately 530 patients meet these criteria.**

- As described in the SUPPORT Neuroimaging and Neurodevelopmental outcome secondary, these patients will have had two CUS (early: 4-14 days of age; late: 35-42 weeks and within 5 days of MRI) and a brain MRI at 35-42 weeks.
    - The CUS with the most severe abnormalities (the "worst" CUS) will be used in comparative analyses
- Estimated cohort size at the time of neurodevelopmental follow-up
    - Follow-up at 18-22 months (ongoing)
        - Estimate 3% death after discharge, 10% loss to F-U:
            - **Cohort=~460 patients**
    - Follow-up at 6½ - 7½ years
        - Estimate additional 20% loss to follow-up:
            - **Cohort = 370 patients**

Design:

- This study is a long-term cognitive, neuromotor, functional, executive function, behavioral assessment of the SUPPORT Neuroimaging cohort at school age (6 ½ - 7 ½ years). **No further neuroimaging is being proposed**.
- Visit at 6½ - 7½ years:
    - The visit battery was assembled and revised after extensive discussions with Protocol Review Subcommittee, Extended SUPPORT Neuroimaging and Neurodevelopmental Outcomes Subcommittee, external advisory reviewers, NRN Follow-up PI group, NRN site psychologists, and evaluation of the challenges and successes of the Extended Hypothermia Follow-up study. The following issues were particularly addressed:
        - Length of visit: Tests and questionnaires were chosen to balance the need for robust neurodevelopmental evaluation, but remain within the confines of a reasonable academic study visit period.
        - Age at visit: Due to differences in age at school start across the U.S., as well as the fact that the WISC-IV "floor" is at 6 years 0 months, there was strong concern that a 6-7 year window would be suboptimal. Therefore, the follow-up window for this study is 6 ½ - 7 ½ years, which will hopefully ameliorate the potential for insufficient sensitivity of WISC-IV for low functioning children at very young ages, and allow for more consistent school exposure across the cohort.
        - Language for tests and questionnaires: There was consensus that tests and questionnaires should be available and normed in Spanish, particularly the instrument used for the cognitive evaluation (primary outcome). It is noted that the NEPSY-II is not available in Spanish. However, site "credit" for a visit will not be linked to attempt of the NEPSY-II in the case of Spanish-speaking children. Furthermore, the BRIEF (parent questionnaire) is available in Spanish, providing some input on the child's executive function.
    - Following is the test and questionnaire grid; note that the child testing and parent questionnaires can be administered simultaneously. Furthermore, the "Break" as presented is a suggested timing. It is understood that each child is an individual, and the NRN site psychologist will determine timing and number of breaks throughout the visit for that particular child's needs.

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CHILD ASSESSMENTS

Test/questionnaire	**Estimated time** **AGE RANGE**	**Spanish version?** **Links to product sites**
ASSESSMENTS		
Check in: Wt, Ht, HC	~10 min	
WISC-IV *	~45-60 min **6 yr 0 months – 16 yr 11 months**	YES http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&Mode=detail&Leaf=avpproducts
Movement-ABC –II *Manual dexterity, Aiming and Catching, Balance*	20-30 min **3-12 years**	Interpreter if needed http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308
Woodcock-Johnson III (ACH) Letter-Word Identification Calculation	~15 minutes **2 years -90+ years**	YES = "Bateria III" http://www.riverpub.com/products; http://www.riverpub.com/products/wjIIIAchievement/details.html
BREAK		
NEPSY II subtests *Executive function domain* Auditory Attention/Response set Inhibition *Visuospatial domain* Design Copying Arrows *Memory* Memory for Names	~25 min **Auditory Attention/Response (5-16 yrs); Inhibition (5-12); Design copying (3-16); Arrows (5-16); Memory for names (5-16)**	No
Neurologic exam (for cerebral palsy)	~15 min	Interpreter if needed
Functional *GMFCS* *Bimanual Fine Motor Function*	5 min **GMFCS – 6-12 yr** **BFMF – 4 yrs and older**	Interpreter if needed; http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf

- * Pediatric Evaluation of Disability Inventory (PEDI)*
  - For children unable to be tested by the WISC-IV due to severe neurodevelopmental impairment, the PEDI will be administered.

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PARENT QUESTIONNAIRES

Test/questionnaire	Estimated time AGE RANGE	Spanish version? Links to product site
Medical history/SES/living arrangement	15 min	Interpreter if needed
QUICCC-R	5-10 min **2-18 years**	YES; http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF
PedsQL (Parent)	5-10 min **versions - 2-4, 5-7, 8-12, 13-18 yrs**	YES; http://www.pedsql.org/
Strengths and Difficulties Questionnaire (SDQ) (Parent)	5-10 min **4-10 yrs**	YES; http://www.sdqinfo.com/
Conners Rating Scale (Parent) (ADHD or Short form only)	10 min **6 yr-17 yr 11 months**	YES; http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&Mode=scoring&Leaf=Conners_3_SF#3
Social Communication Questionnaire (Parent; Lifetime form)	10 min **Over 4 years**	YES; http://portal.wpspublish.com/portal/page?_pageid=53,70432&_dad=portal&_schema=PORTAL
Behavior Rating Inventory of Executive Function (BRIEF-Parent version)	15 min **5-18 yrs**	YES; http://www3.parinc.com/products/product.aspx?Productid=BRIEF

Statistical considerations:

Analyses:

- Since we are concerned with the relative diagnostic power of the MRI versus the CUS, an appropriate statistical methodology is an ROC analysis. This analysis is based on the sensitivity and specificity and compares the diagnostic power over the entire range of the diagnostic variable(s) and thus negates the need to select "cut points". The analysis related to the primary hypothesis will compare the ROC curves for a predictive model based on the MRI data versus a predictive model based on the CUS data. The WISC-IV < 70 or death after discharge will be the primary outcome variable. The WISC-IV < 70 among survivors will also be evaluated as an outcome variable.
    - We will conduct the ROC analysis with WISC-IV <70 (or death after discharge) as the outcome when either MRI or CUS data are in the predictive model and will compare the ROCs for the two models for statistical significance. Since MRI and CUS are done on the same subjects, it will not be necessary to adjust for risk factors in comparing the two tools.
        - In separate analyses, NRN center may be entered as a variable to assess the confounding effects of site. Although CUS and MRI are

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centrally-read, and significant attempts to ensure reliability and consistency of WPPSI evaluation across sites will be made, unanticipated and unmeasurable differences between sites in quality of neuroimaging or in WISC-IV administration *may* confound analyses;

- We will conduct the ROC analysis with WISC-IV <70 (or death after discharge) as the outcome when only "traditional variables" (non-neuroimaging variables) are the only variables in the model;
- We will also do the ROC analysis that compares the contribution of MRI and CUS to the prediction of outcome above and beyond that of the traditional clinical variables.
- Will also do the ROC analysis that compares the incremental value of adding MRI to the prediction of outcome above and beyond that of traditional clinical variables plus CUS
- Logistic regression analysis will be used to compare 6½ - 7½ year neurodevelopmental outcomes (or death after discharge) between oxygenation and ventilation SUPPORT randomized groups. These analyses will be adjusted for baseline risk variables.
  - The baseline risk variables pre-specified for adjustment in the main SUPPORT trial are the stratification variables (NRN site and GA group). In comparing 6½ - 7½ year outcomes between SUPPORT randomized groups, we plan to adjust only for these variables in our initial approach. However, since the Neuroimaging cohort may not be representative of the originally randomized study cohort, we will investigate differences between the 6½ - 7½ year follow-up groups and consider a subsequent level analysis adding other factors if there is an indication of systematic differences.
- Local vs. central neuroimaging secondary analyses: As recommended by the Protocol Review Subcommittee, secondary analyses including evaluation of local MRI reading will be undertaken.
  - Local CUS readings are already collected in the SUPPORT or GDB database; local MRI readings (print-out of final local read with study ID and center written on the document, but patient identifiers removed or blacked out) will be collected.
  - Accuracy of local compared with central neuroimaging interpretation will be performed by sensitivity and specificity analyses (Hintz #3).
  - Additional analyses will compare capability of local MRI read and central MRI read to predict 6½ - 7½ year outcomes by ROC analysis.

- "Traditional non-neuroimaging variables": Based on previous investigations assessing the associations of demographic, socioeconomic, perinatal, and neonatal factors with school-age outcomes (Taylor, Doyle #2), we propose the following non-neuroimaging variables will be used in model development; other variables may be considered.
  - Center
  - Gestational age
  - Race
  - Gender
  - Multiple gestation
  - Maternal education level (at baseline)

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- [SUPPORT treatment group]
- Sepsis or meningitis
- NEC
- BPD
- Postnatal steroids
- ROP stage III or more severe
- Length of initial hospital stay (EGA adjusted, i.e., PCA at discharge)
- Any surgery during initial hospitalization

Sample size and power analysis (Primary Hypothesis):

- The sample sizes in the table below are based on formulae for two correlated ROCs (e.g. two ROCs based on the same sample). According to the discussion in the protocol above, we assume that around 370 infants will be available for the 6½ - 7½ year IQ evaluation, assuming ~20% loss to follow-up between 18-22 months and school-age. For a two-tailed test at the 0.05 level of significance and assuming the lowest area under the ROC curve (AUC) for the MRI and the CUS is 75%, an even more conservative estimate of 350 children would produce the powers in the table below for an array of detectable increases in the AUC and prevalence of outcome.

POWER FOR SELECTED INCREASES FROM 75% IN THE AUC OF THE ROC AND PREVALENCES OF THE PRIMARY OUTCOME:
SAMPLE SIZE = 350

AUC Inc. / Outcome P	5%	6%	7%	8%	9%	10%
20%	31%	43%	55%	67%	77%	86%
25%	37%	50%	64%	76%	85%	92%
30%	42%	56%	70%	81%	90%	95%

Hence, if the prevalence of the primary outcome is as low as 20% a conservative sample size of 350 would identify an AUC increase of 10% with reasonable power (86%); if the prevalence is 30%, the detectable increase would be 8% (with power 80%).

Budget: The costs of this proposed follow-up study would span over several years. The first enrolled patient will reach the 6th birthday on 05/10/2011, thus the first window will open 11/10/2011. **It is estimated that 6½ - 7½ year follow-up windows will extend from November 2011 to late 2016.** A range of costs for some subcategories has been provided for loss to follow-up rates between 18-22 months to 6 ½ - 7 ½ years of 10% - 20%.

- Tracking: Similar to the Extended Follow-up of the Hypothermia Trial, tracking will be critical to ensure the best possible follow-up. **Tracking tools and forms have already been developed and launched. RTI is sending tracking reminders to sites.** Because of the importance robust school-age follow-up rates, considerable

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funds have been budgeted for tracking contacts. The following are suggested contact schedules, although each site will implement specific tracking and contacts appropriate for their patients:
  - Between 18-22 month and 3-4 years: <u>at least</u> 2 phone or other family contacts/ tracking events
  - Between 3-4 years and 6½ - 7½ years: <u>at least</u> 4 phone or other family contacts/ tracking events
  - **$420 per child has been budgeted for tracking.** Release of tracking funds will be contingent on completion of the SEF01 form (tracking form for 18-22 month to 3-4 year contacts).
  - **Total**: **$155,400 – $174,300**
- <u>Consents</u>: Consent to contact families for possible 6½ - 7½ year follow-up is currently being sought at the 18-22 month visit. Tracking will then commence as noted above. Formal signed consent will be obtained for the majority of the cohort at the time of the 6½ - 7½ year follow-up visit. It is expected that the consent process will take ~1/2 hour (@$35/hour).
  - 14 patients had already been seen in 18-22 month follow-up prior to Dr. Higgins' announcement to NRN site PI's and Follow-up PI's to request to maintain contact. These patients will require some additional time for tracking/consent. We expect that the consent process will take ~1 hour in these cases (@$35/hour).
  - **Total: $6475-$7263**
- <u>Local MRI read:</u> We estimate that relatively little time (~1/2 hour per MRI x $35/hour) will be required to print out/copy final local MRI report, black out patient identifiers, and write in Center number and subject number. These documents will then be sent to RTI.
  - **Total: $9275**
- <u>Training and assuring reliability:</u> The first enrolled SUPPORT Neuroimaging cohort patient will reach the extended follow-up window opening in November 2011. However, there are just 10 patients in the first "wave" with the majority of patient windows not opening until February 2012. Furthermore, given the length of the SUPPORT trial, the final enrolled patients will have 6½ - 7½ year follow-up windows that extend to late 2016. Thus, the total cohort follow-up period will span approximately 5 years. To ensure ongoing training and achieve the best possible reliability for the primary outcome measure (WISC-IV), the following training and reliability assessments have been determined:
  - Training sessions: We propose adding another WISC-IV training session for all sites midway through the follow-up (late 2013 or early 2014). As with the Extended Hypothermia Follow-up, these training sessions will also include training in other components of the follow-up exam, including the NEPSY-II and PEDI. 15 sites are participating in the SUPPORT Neuroimaging secondary, but the 15th site (Emory) will not have patients reaching the 6th birthday until after 2013. We have also added incrementally to the cost per site in 2013 to adjust for inflation.
    - First training session (Fall 2011): $3200 x 14 sites =$44,800
    - Second training session (late 2013): $3400 x 15 sites =$51,000
  - Reliability assessment: In response to Protocol Review Subcommittee comments, we propose ongoing routine exam taping to be sent from

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participating sites to one of two GOLD STANDARD WISC-IV psychologists. After training and subsequent certification by one taped exam on a non-study patient, the first 3 exams from each site be taped and sent for review and comment, then approximately every 10th exam. This approach will necessitate a DVD recorder to be purchased by each site. We estimate that 3 hours will be required to review and comment upon each WISC-IV exam at $60/hour. Gold standard psychologists will assure that turn-around for comments on these exams be rapid so that sites can incorporate feedback in subsequent scheduled patients' visits. Thus, the budget would reflect the following:

- DVD recorders for each site: $350 x 15 sites = $5250
- Review and comment on certification exam =
  - 1 x 15 sites x 3 hours x $60/hr = $2700
- Review 1st 3 exams from each site =
  - 3x15 site x 3 hrs x $60/hr = $8100
- Review of every 10th exam: Dependent on follow-up numbers:
  - Approximately 30 additional exams x 3 hrs x $60/hr = $5400

- **Total = $117,250**

- 6½ - 7½ year visit costs:
  - $1200 per child has been budgeted for the study visit
  - **Total = $444,000-$498,000**

TOTAL BUDGET ESTIMATE: $732,400 - $806,088 *plus RTI costs*

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Extended Follow-up visit battery August 2009
School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

Test/questionnaire	Estimated time AGE RANGE	Spanish version?
[redacted]		
Check in: Wt, Ht, HC	~10 min	
WISC-IV	~45-60 min **6 yr 0 months – 16 yr 11 months**	YES http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&Mode=detail&Leaf=avpproducts
Movement-ABC –II	20-30 min **3-12 years**	Interpreter if needed http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308
Woodcock-Johnson III (ACH) **Letter-Word Identification** **Calculation**	~15 minutes **2 years -90+ years**	YES = "Bateria III" http://www.riverpub.com/products; http://www.riverpub.com/products/wjIIIAchievement/details.html
BREAK		
NEPSY II subtests ***Executive function domain*** **Auditory Attention/Response set** **Inhibition** ***Visuospatial domain*** **Design Copying** **Arrows** ***Memory*** **Memory for Names**	~25 min **Auditory Attention/Response (5-16 yrs); Inhibition (5-12); Design copying (3-16); Arrows (5-16); Memory for names (5-16)**	No
Neurologic exam	~15 min	Interpreter if needed
Functional *GMFCS* *Bimanual Fine Motor Function*	5 min **GMFCS – 6-12 yr** **BFMF – 4 yrs and older**	Interpreter if needed; http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf

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Extended Follow-up visit battery August 2009
School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

Test/questionnaire	Estimated time AGE RANGE	Spanish version?
PARENT QUESTIONNAIRES		
Medical history/SES/living arrangement	15 min	Interpreter if needed
QUICCC-R	5-10 min **2-18 years**	YES; http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF
PedsQL (Parent)	5-10 min **versions - 2-4 yrs, 5-7, 8-12, 13-18**	YES; http://www.pedsql.org/
Strengths and Difficulties Questionnaire (SDQ) (Parent)	5-10 min **version 4-10 yr**	YES; http://www.sdqinfo.com/
Conners Rating Scale (Parent) (ADHD or Short only)	10 min **6 yr-17 yr 11 months**	YES; http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&Mode=scoring&Leaf=Conners_3_SF#3
Social Communication Questionnaire (Parent; Lifetime form)	10 min **Over 4 years**	YES; http://portal.wpspublish.com/portal/page?_pageid=53,70432&_dad=portal&_schema=PORTAL
Behavior Rating Inventory of Executive Function (BRIEF-Parent)	15 min **5-18 yrs**	YES; http://www3.parinc.com/products/product.aspx?Productid=BRIEF

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From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Pulmonary outcomes at 6-7 years
Date: Monday, October 05, 2009 11:30:10 AM

Hi Rose,

Yes, I am writing it. I just received comments back from Richard and will get it to you soon. Is there a timeline that I should follow?

Bill asked whether this is the sort of study that could be submitted as an RO1 to offset network costs and provide investigator support for me. Is that a viable option (depending on its fundability of course).

Thanks

Tim

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 05, 2009 8:46 AM
To: 'Richard Ehrenkranz'; Stevens, Timothy
Subject: Pulmonary outcomes at 6-7 years

Hi,
Were you still planning on submitting a proposal to the Network for pulmonary outcomes (concept approved) for SUPPORT at school age?

let me know

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Ophthalmology
Date: Monday, October 05, 2009 10:59:01 AM

Hi Rose,
Oct. 20 would be fine. Let me know what time, (not before 10:30am Eastern time please)

I will send a message to Dr. Wallace about the adjudication and communication to come from you or RTI. Actually, who should I say?

I would like to remain involved in how this is set up and done. It that possible? I did have quite the experience with this when EMMES Corp. set it up for the STOP-ROP study.

Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 05, 2009 5:43 AM
To: Phelps, Dale
Cc: Zaterka-Baxter, Kristin; Abhik Das (adas@rti.org); 'Gantz, Marie'
Subject: SUPPORT Ophthalmology

Dale
Can we set up a call for ophthalmology exam adjudication for the SUPPORT study (October 20 would be good if you are available). Also – Can we correspond directly with Dr. Wallace at Duke?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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higginsr@mail.nih.gov

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From:	Zaterka-Baxter, Kristin
To:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	FW: NIH Hispanic Race by Gender
Date:	Monday, October 05, 2009 9:09:40 AM
Attachments:	CenterHispby Gender.zip Enroll2008toRose.zip

Is this what you need?
Thanks,
Kris

From: Auman, Jeanette O.
Sent: Tuesday, February 03, 2009 12:19 PM
To: Zaterka-Baxter, Kristin
Subject: FW: NIH Hispanic Race by Gender

Here you go!

From: Zaterka-Baxter, Kristin
Sent: Tuesday, February 03, 2009 12:08 PM
To: Auman, Jeanette O.
Subject: FW: NIH Hispanic Race by Gender

From: Zaterka-Baxter, Kristin
Sent: Thursday, January 31, 2008 9:37 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: NIH Hispanic Race by Gender

Hi,
Didn't know how separate you needed the tables so in the zip file they are separated by site and protocol and the adobe files have all protocols by center.
Thanks,
Kris

Kris Zaterka-Baxter
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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Duke University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	1	4	5
Unknown or Not Reported	1	1	2
Total	2	6	8

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Duke University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	2	4
Total	2	2	4

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Duke University

Table of race by gender		
race	gender	
Frequency	Male	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Emory University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	1	2
Total	1	1	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Emory University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	2	0	2
White	0	1	1
Unknown or Not Reported	5	7	12
Total	7	8	15

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Emory University

Table of race by gender		
race	gender	
Frequency	Male	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=Indiana University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Indiana University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	3	5
Total	2	3	5

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Indiana University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	12	14	26
Total	12	15	27

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=Indiana University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	2	0	2
Total	2	1	3

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

GDB

Center=University of Iowa

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Asian	0	1	1
White	4	4	8
Total	4	5	9

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=U of Miami

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	3	0	3
White	23	13	36
Total	26	13	39

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of New Mexico

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
American Indian	0	1	1
White	24	34	58
Total	24	35	59

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Neonatal Research Network

2007 Race/Gender Tables (randomized 1/1-11/30)

Hispanic subjects ONLY (table 3)

Support Protocol

Center ID number=University of New Mexico

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	2	4
Total	2	2	4

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=University of New Mexico

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	2	4
Total	2	2	4

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
EOS Protocol

Center ID number=University of New Mexico

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	3	3	6
Total	3	3	6

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Inositol

Center=University of New Mexico

Table of race by gender		
race	gender	
Frequency	Male	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Rochester

Table of race by gender		
race	gender	
Frequency	Male	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Stanford University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Native Hawaiian	1	0	1
White	29	29	58
Total	30	29	59

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Stanford University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	10	8	18
Total	10	8	18

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Stanford University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	5	6	11
Total	5	6	11

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=Stanford University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=Stanford University

Table of race by gender		
race	gender	
Frequency	Male	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
EOS Protocol

Center ID number=Stanford University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	3	1	4
Total	3	1	4

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Neonatal Research Network
2007 Race/Gender Tables (followed 1/1-11/30)
Hispanic subjects ONLY (table 3)
Hypothermia Extended FU

Center:=Stanford

Table of race by gender		
race	gender	
Frequency	Male	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Tufts University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	1	1	2
White	22	21	43
Total	23	22	45

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Tufts University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	3	7	10
Total	3	8	11

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=Tufts University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=Tufts University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
EOS Protocol

Center ID number=Tufts University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Unknown or Not Reported	1	1
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of Alabama

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	1	0	1
White	5	10	15
Total	6	10	16

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=University of Alabama

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	2	4
Total	2	2	4

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=University of Alabama

Table of race by gender		
race	gender	
Frequency	Female	Total
Black	1	1
Total	1	1

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=University of Alabama

Table of race by gender		
race	gender	
Frequency	Female	Total
Black	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=San Diego

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	14	13	27
Total	14	13	27

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=USC San Diego

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	3	3	6
Total	3	3	6

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
American Indian	2	0	2
White	55	58	113
Total	57	58	115

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	12	10	22
Total	12	10	22

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	7	12	19
Total	7	12	19

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	5	4	9
Total	5	4	9

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	1	2
Total	1	1	2

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
EOS Protocol

Center ID number=University of Texas-Dallas

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	5	7	12
Total	5	7	12

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Neonatal Research Network
2007 Race/Gender Tables (followed 1/1-11/30)
Hispanic subjects ONLY (table 3)
Hypothermia Extended FU

Center:=Dallas

Table of race by gender		
race	gender	
Frequency	Male	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of Tex-Houston

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	3	0	3
White	18	29	47
Total	21	29	50

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=University of Tex-Houston

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	18	17	35
Total	18	17	35

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=University of Tex-Houston

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	3	4
Total	1	3	4

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=University of Tex-Houston

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	1	0	1
White	2	5	7
Total	3	5	8

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=University of Tex-Houston

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	1	0	1
White	1	1	2
Total	2	1	3

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of Utah

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
American Indian	1	0	1
Black	1	1	2
White	8	9	17
More than 1 race reported	0	1	1
Unknown or Not Reported	20	15	35
Total	30	26	56

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=University of Utah

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Unknown or Not Reported	1	1
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=University of Utah

Table of race by gender		
race	gender	
Frequency	Male	Total
More than 1 race reported	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Wake Forest

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	5	2	7
Total	5	2	7

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Wayne State University

Table of race by gender		
race	gender	
Frequency	Female	Total
Black	2	2
White	2	2
Total	4	4

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Wayne State University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Wayne State University

Table of race by gender		
race	gender	
Frequency	Female	Total
Black	1	1
White	1	1
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=Wayne State University

Table of race by gender		
race	gender	
Frequency	Female	Total
Black	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
EOS Protocol

Center ID number=Wayne State University

Table of race by gender		
race	gender	
Frequency	Male	Total
Unknown or Not Reported	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Inositol

Center=Wayne State University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Yale University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	2	2	4
White	22	15	37
Total	24	17	41

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=Yale University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	5	3	8
Total	5	4	9

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Yale University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	2	2
Total	2	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Candida Protocol

Center=Yale University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	1	2
Total	1	1	2

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
Physiological Def of BPD

Center=Yale University

Table of race by gender		
race	gender	
Frequency	Female	Total
White	1	1
Total	1	1

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Neonatal Research Network
2007 Race/Gender Tables (followed 1/1-11/30)
Hispanic subjects ONLY (table 3)
Hypothermia Extended FU

Center:=Yale

Table of race by gender		
race	gender	
Frequency	Male	Total
White	1	1
Total	1	1

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

GDB

Center=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	2	2
White	21	19	40
Unknown or Not Reported	1	1	2
Total	22	22	44

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

18 month Follow-Up

Center=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	1	1	2
Total	1	2	3

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Neonatal Research Network

2007 Race/Gender Tables (randomized 1/1-11/30)

Hispanic subjects ONLY (table 3)

Support Protocol

Center ID number=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	3	2	5
Total	3	2	5

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

Candida Protocol

Center=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
Black	0	1	1
White	4	0	4
Unknown or Not Reported	0	1	1
Total	4	2	6

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

Inositol

Center=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	1	2
Total	1	1	2

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Neonatal Research Network

2007 Race/Gender Tables (born 1/1-11/30)

Hispanic subjects ONLY (table 3)

Physiological Def of BPD

Center=Brown University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	4	2	6
Unknown or Not Reported	0	1	1
Total	4	3	7

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=Case Western University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	4	2	6
Total	4	2	6

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Neonatal Research Network
2007 Race/Gender Tables (randomized 1/1-11/30)
Hispanic subjects ONLY (table 3)
Support Protocol

Center ID number=Case Western University

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	2	2	4
Total	2	2	4

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
GDB

Center=University of Cincinnati

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	8	4	12
Total	8	4	12

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Neonatal Research Network
2007 Race/Gender Tables (born 1/1-11/30)
Hispanic subjects ONLY (table 3)
18 month Follow-Up

Center=University of Cincinnati

Table of race by gender			
race	gender		
Frequency	Female	Male	Total
White	1	2	3
Total	1	2	3

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Inclusion Enrollment Report for the GDB Study for Center 26

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	13	22	0	35
Ethnic - Not Hisp or Latino	16	12	0	28
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	29	34	0	63
Amer Indian/Alaska	4	6	0	10
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	25	28	0	53
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	29	34	0	63
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	13	22	0	35
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	13	22	0	35

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 26

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	0	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	1	0	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	0	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Support Study for Center 26

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	1	0	3
Ethnic - Not Hisp or Latino	4	0	0	4
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	6	1	0	7
Amer Indian/Alaska	1	0	0	1
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	5	1	0	6
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	6	1	0	7
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	1	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	1	0	3

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Inclusion Enrollment Report for the Early Onset Sepsis Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	21	32	0	53
Ethnicity: Not Hisp or Latino	32	53	1	86
Ethnicity: Unknown	5	5	0	10
Ethnicity: Total of All Subjects	58	90	0	149
Amer Indian/Alaska	0	0	1	1
Asia	1	4	0	5
Hawaiian or Other Pacific	0	1	0	1
Black or African Amer	17	25	0	42
White	35	58	0	93
More than One	2	1	0	3
Unknown or Not Reported	3	1	0	4
Racial Categories: Total of all	58	90	1	149
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	3	0	4
Hispanic: White	19	29	0	48
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	0	0	1
Hispanic: Racial Categories: Total of al	21	32	0	53

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Inclusion Enrollment Report for the Follow-up Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	72	74	0	146
Ethnicity: Not Hisp or Latino	335	325	2	662
Ethnicity: Unknown	2	2	0	4
Ethnicity: Total of All Subjects	409	401	0	812
Amer Indian/Alaska	0	2	0	2
Asia	8	10	1	19
Hawaiian or Other Pacific	1	0	0	1
Black or African Amer	184	164	0	348
White	211	220	1	432
More than One	2	2	0	4
Unknown or Not Reported	3	3	0	6
Racial Categories: Total of all	409	401	2	812
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	1	1	0	2
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	5	2	0	7
Hispanic: White	64	70	0	134
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	2	1	0	3
Hispanic: Racial Categories: Total of al	72	74	0	146

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Inclusion Enrollment Report for the GDB Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	163	172	2	337
Ethnicity: Not Hisp or Latino	684	713	2	1399
Ethnicity: Unknown	49	62	0	111
Ethnicity: Total of All Subjects	896	947	0	1847
Amer Indian/Alaska	6	9	0	15
Asia	39	31	1	71
Hawaiian or Other Pacific	1	6	0	7
Black or African Amer	333	361	0	694
White	490	528	3	1021
More than One	5	4	0	9
Unknown or Not Reported	22	8	0	30
Racial Categories: Total of all	896	947	4	1847
Hispanic: Amer Indian/Alaska	1	1	0	2
Hispanic: Asia	0	1	1	2
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	11	6	0	17
Hispanic: White	134	156	1	291
Hispanic: More than One	0	1	0	1
Hispanic: Unknown or Not Reported	17	7	0	24
Hispanic: Racial Categories: Total of al	163	172	2	337

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	6	7	0	13
Ethnicity: Not Hisp or Latino	14	12	0	26
Ethnicity: Unknown	0	0	0	0
Ethnicity: Total of All Subjects	20	19	0	39
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	5	3	0	8
White	15	16	0	31
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	20	19	0	39
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	6	7	0	13
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	7	0	13

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Inclusion Enrollment Report for the Late Hypothermia Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	2	1	0	3
Ethnicity: Not Hisp or Latino	3	2	0	5
Ethnicity: Unknown	1	3	0	4
Ethnicity: Total of All Subjects	6	6	0	12
Amer Indian/Alaska	1	0	0	1
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	3	4	0	7
More than One	0	0	0	0
Unknown or Not Reported	0	2	0	2
Racial Categories: Total of all	6	6	0	12
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	1	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	1	0	3

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Inclusion Enrollment Report for the Physiologic Definition Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	2	7	0	9
Ethnicity: Not Hisp or Latino	31	33	0	64
Ethnicity: Unknown	0	1	0	1
Ethnicity: Total of All Subjects	33	41	0	74
Amer Indian/Alaska	0	0	0	0
Asia	1	1	0	2
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	13	11	0	24
White	18	28	0	46
More than One	1	1	0	2
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	33	41	0	74
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	7	0	9
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	7	0	9

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Inclusion Enrollment Report for the Support Study for ALL Centers

Categories	Females	Males	Unknown	total
Ethnicity: Hisp or Latino	32	36	0	68
Ethnicity: Not Hisp or Latino	121	131	0	252
Ethnicity: Unknown	7	22	0	29
Ethnicity: Total of All Subjects	160	189	0	349
Amer Indian/Alaska	1	1	0	2
Asia	3	3	0	6
Hawaiian or Other Pacific	0	1	0	1
Black or African Amer	58	75	0	133
White	95	107	0	202
More than One	1	1	0	2
Unknown or Not Reported	2	1	0	3
Racial Categories: Total of all	160	189	0	349
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	3	1	0	4
Hispanic: White	27	34	0	61
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	2	1	0	3
Hispanic: Racial Categories: Total of al	32	36	0	68

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	2	1	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	1	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	1	1	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	1	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Follow-up Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	24	18	0	42
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	25	18	0	43
Amer Indian/Alaska	0	1	0	1
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	18	9	0	27
White	7	8	0	15
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	25	18	0	43
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	0	0	1
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the GDB Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	0	0	2
Ethnic - Not Hisp or Latino	40	51	0	91
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	42	51	0	93
Amer Indian/Alaska	0	0	0	0
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	30	37	0	67
White	12	13	0	25
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	42	51	0	93
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	2	0	0	2
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	0	0	2

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	3	0	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	0	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	2	0	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	0	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	4	1	0	5
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	1	0	5
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	1	0	4
White	1	0	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	1	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Support Study for Center 3

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	13	11	0	24
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	14	11	0	25
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	7	8	0	15
White	7	3	0	10
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	14	11	0	25
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	0	0	1
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	7	13	0	20
Ethnic - Not Hisp or Latino	1	2	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	8	15	0	23
Amer Indian/Alaska	0	0	0	0
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	1	0	2
White	7	13	0	20
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	8	15	0	23
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	7	13	0	20
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	7	13	0	20

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the Follow-up Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	11	12	0	23
Ethnic - Not Hisp or Latino	11	5	0	16
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	22	17	0	39
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	10	5	0	15
White	12	12	0	24
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	22	17	0	39
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	11	12	0	23
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	11	12	0	23

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the GDB Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	27	36	0	63
Ethnic - Not Hisp or Latino	20	27	0	47
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	47	63	0	110
Amer Indian/Alaska	0	0	0	0
Asia	2	4	0	6
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	16	21	0	37
White	29	38	0	67
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	47	63	0	110
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	27	36	0	63
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	27	36	0	63

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	3	0	3
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	3	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	3	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	3	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	3	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	3	0	3

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the Late Hypothermia Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	1	0	1
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	2	0	2
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	3	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	0	2	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	3	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	2	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	2	0	2

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Inclusion Enrollment Report for the Support Study for Center 4

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	5	9	0	14
Ethnic - Not Hisp or Latino	1	6	0	7
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	6	15	0	21
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	5	0	6
White	5	10	0	15
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	6	15	0	21
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	5	9	0	14
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	5	9	0	14

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	0	1	1
Ethnic - Unknown	4	4	0	8
Ethnicity: Total of All Subjects	4	4	0	9
Amer Indian/Alaska	0	0	1	1
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	2	0	5
White	1	2	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	4	1	9
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Follow-up Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	1	0	2
Ethnic - Not Hisp or Latino	20	31	0	51
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	21	32	0	53
Amer Indian/Alaska	0	0	0	0
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	19	27	0	46
White	2	4	0	6
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	21	32	0	53
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	1	0	1
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	1	0	2

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Inclusion Enrollment Report for the GDB Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	2	0	0	2
Ethnic - Unknown	46	60	0	106
Ethnicity: Total of All Subjects	48	60	0	108
Amer Indian/Alaska	0	1	0	1
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	36	53	0	89
White	11	6	0	17
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	48	60	0	108
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	3	2	0	5
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	2	0	6
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	2	1	0	3
White	2	1	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	2	0	6
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	0	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	1	0	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	0	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Support Study for Center 5

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	7	21	0	28
Ethnicity: Total of All Subjects	7	21	0	28
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	6	20	0	26
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	7	21	0	28
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	1	0	2
Ethnic - Not Hisp or Latino	7	6	0	13
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	8	7	0	15
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	5	6	0	11
White	2	1	0	3
More than One	0	0	0	0
Unknown or Not Reported	1	0	0	1
Racial Categories: Total of all	8	7	0	15
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	1	0	1
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	0	0	1
Hispanic: Racial Categories: Total of al	1	1	0	2

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Inclusion Enrollment Report for the Follow-up Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	2	0	4
Ethnic - Not Hisp or Latino	26	23	0	49
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	28	25	0	53
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	21	21	0	42
White	6	3	0	9
More than One	0	0	0	0
Unknown or Not Reported	1	1	0	2
Racial Categories: Total of all	28	25	0	53
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	1	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	1	0	2
Hispanic: Racial Categories: Total of al	2	2	0	4

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Inclusion Enrollment Report for the GDB Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	13	3	0	16
Ethnic - Not Hisp or Latino	51	38	0	89
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	64	41	0	105
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	49	32	0	81
White	1	6	0	7
More than One	0	0	0	0
Unknown or Not Reported	13	3	0	16
Racial Categories: Total of all	64	41	0	105
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	13	3	0	16
Hispanic: Racial Categories: Total of al	13	3	0	16

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Support Study for Center 9

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	1	0	3
Ethnic - Not Hisp or Latino	15	8	0	23
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	17	9	0	26
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	14	5	0	19
White	1	3	0	4
More than One	0	0	0	0
Unknown or Not Reported	2	1	0	3
Racial Categories: Total of all	17	9	0	26
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	2	1	0	3
Hispanic: Racial Categories: Total of al	2	1	0	3

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	2	0	2
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	2	0	2
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	2	0	2
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Support Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	10	14	0	24
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	10	14	0	24
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	4	5	0	9
White	6	9	0	15
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	10	14	0	24
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	4	7	0	11
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	7	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	2	2	0	4
White	2	5	0	7
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	7	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	2	2	0	4
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	2	0	4
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	1	2	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	2	0	4
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	4	0	10
Ethnic - Not Hisp or Latino	114	110	0	224
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	120	114	0	234
Amer Indian/Alaska	0	0	0	0
Asia	2	2	0	4
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	39	36	0	75
White	77	75	0	152
More than One	0	1	0	1
Unknown or Not Reported	2	0	0	2
Racial Categories: Total of all	120	114	0	234
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	6	3	0	9
Hispanic: More than One	0	1	0	1
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	4	0	10

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Follow-up Study for Center 11

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	36	39	0	75
Ethnic - Unknown	1	0	0	1
Ethnicity: Total of All Subjects	38	39	0	77
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	12	17	0	29
White	25	22	0	47
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	38	39	0	77
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	4	2	0	6
Ethnic - Not Hisp or Latino	5	5	0	10
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	9	7	0	16
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	2	0	5
White	6	5	0	11
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	9	7	0	16
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	4	2	0	6
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	4	2	0	6

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Inclusion Enrollment Report for the Support Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	7	7	0	14
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	7	7	0	14
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	2	0	5
White	4	5	0	9
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	7	7	0	14
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	7	4	0	11
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	7	4	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	2	0	5
White	4	2	0	6
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	7	4	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	2	1	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	1	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	2	1	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	1	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	10	6	0	16
Ethnic - Not Hisp or Latino	47	66	1	114
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	57	72	0	130
Amer Indian/Alaska	0	0	0	0
Asia	1	1	0	2
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	21	25	0	46
White	35	46	1	82
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	57	72	1	130
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	10	6	0	16
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	10	6	0	16

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Inclusion Enrollment Report for the Follow-up Study for Center 12

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	2	0	3
Ethnic - Not Hisp or Latino	26	21	0	47
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	27	23	0	50
Amer Indian/Alaska	0	0	0	0
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	12	6	0	18
White	15	16	0	31
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	27	23	0	50
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	2	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	2	0	3

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	4	6	0	10
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	6	0	10
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	2	0	2
White	4	4	0	8
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	6	0	10
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Support Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	1	0	3
Ethnic - Not Hisp or Latino	6	6	0	12
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	8	7	0	15
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	3	0	6
White	5	4	0	9
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	8	7	0	15
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	1	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	1	0	3

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	2	1	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	1	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	2	0	0	2
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	1	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	0	0	0
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	1	0	1
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	12	9	0	21
Ethnic - Not Hisp or Latino	43	54	0	97
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	55	63	0	118
Amer Indian/Alaska	0	0	0	0
Asia	2	2	0	4
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	22	22	0	44
White	30	39	0	69
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	55	63	0	118
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	3	0	0	3
Hispanic: White	9	9	0	18
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	12	9	0	21

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Inclusion Enrollment Report for the Follow-up Study for Center 13

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	7	0	13
Ethnic - Not Hisp or Latino	22	16	1	39
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	28	23	0	52
Amer Indian/Alaska	0	0	0	0
Asia	0	0	1	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	10	10	0	20
White	17	12	0	29
More than One	0	0	0	0
Unknown or Not Reported	1	1	0	2
Racial Categories: Total of all	28	23	1	52
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	6	7	0	13
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	7	0	13

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Inclusion Enrollment Report for the GDB Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	10	13	0	23
Ethnic - Not Hisp or Latino	51	41	0	92
Ethnic - Unknown	1	1	0	2
Ethnicity: Total of All Subjects	62	55	0	117
Amer Indian/Alaska	0	1	0	1
Asia	0	4	0	4
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	10	8	0	18
White	50	41	0	91
More than One	1	0	0	1
Unknown or Not Reported	1	1	0	2
Racial Categories: Total of all	62	55	0	117
Hispanic: Amer Indian/Alaska	0	1	0	1
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	2	2	0	4
Hispanic: White	7	9	0	16
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	1	0	2
Hispanic: Racial Categories: Total of al	10	13	0	23

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	4	3	0	7
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	5	4	0	9
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	1	0	2
White	4	3	0	7
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	5	4	0	9
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Support Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	5	0	11
Ethnic - Not Hisp or Latino	15	11	0	26
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	21	17	0	38
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	3	0	6
White	18	14	0	32
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	21	17	0	38
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	1	0	2
Hispanic: White	5	4	0	9
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	5	0	11

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	1	0	0	1
Ethnicity: Total of All Subjects	2	0	0	2
Amer Indian/Alaska	1	0	0	1
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	0	0	2
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Follow-up Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	3	0	9
Ethnic - Not Hisp or Latino	28	24	0	52
Ethnic - Unknown	1	2	0	3
Ethnicity: Total of All Subjects	35	29	0	64
Amer Indian/Alaska	0	0	0	0
Asia	1	2	0	3
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	10	6	0	16
White	24	19	0	43
More than One	0	1	0	1
Unknown or Not Reported	0	1	0	1
Racial Categories: Total of all	35	29	0	64
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	2	1	0	3
Hispanic: White	4	2	0	6
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	3	0	9

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	0	0	2
Ethnic - Not Hisp or Latino	0	2	0	2
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	2	0	4
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	2	1	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	2	0	4
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	0	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	0	0	2

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 14

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	3	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	3	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	3	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	3	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	1	0	1
Ethnic - Not Hisp or Latino	0	4	0	4
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	5	0	5
Amer Indian/Alaska	0	0	0	0
Asia	0	3	0	3
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	2	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	5	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	1	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	1	0	1

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	2	0	3
Ethnic - Not Hisp or Latino	2	5	0	7
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	7	0	10
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	4	0	5
White	2	3	0	5
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	7	0	10
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	2	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	2	0	3

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Inclusion Enrollment Report for the Support Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	4	3	0	7
Ethnic - Not Hisp or Latino	7	7	0	14
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	11	10	0	21
Amer Indian/Alaska	0	0	0	0
Asia	2	3	0	5
Hawaiian or Other Pacific	0	1	0	1
Black or African Amer	0	0	0	0
White	9	6	0	15
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	11	10	0	21
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	4	3	0	7
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	4	3	0	7

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	1	0	2
Ethnic - Not Hisp or Latino	1	1	0	2
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	2	0	4
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	1	1	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	2	0	4
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	1	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	1	0	2

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	0	0	2
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	2	0	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	0	0	2
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the GDB Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	11	11	0	22
Ethnic - Not Hisp or Latino	28	30	0	58
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	39	41	0	80
Amer Indian/Alaska	0	0	0	0
Asia	15	9	0	24
Hawaiian or Other Pacific	0	6	0	6
Black or African Amer	3	3	0	6
White	21	23	0	44
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	39	41	0	80
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	11	11	0	22
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	11	11	0	22

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Inclusion Enrollment Report for the Follow-up Study for Center 15

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	7	6	0	13
Ethnic - Not Hisp or Latino	8	14	0	22
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	15	20	0	35
Amer Indian/Alaska	0	0	0	0
Asia	2	4	0	6
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	4	0	5
White	11	12	0	23
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	15	20	0	35
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	1	0	1
Hispanic: White	7	5	0	12
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	7	6	0	13

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Inclusion Enrollment Report for the Follow-up Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	4	0	7
Ethnic - Not Hisp or Latino	45	60	0	105
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	48	64	0	112
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	27	31	0	58
White	21	33	0	54
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	48	64	0	112
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	3	4	0	7
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	3	4	0	7

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Inclusion Enrollment Report for the Support Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	2	0	5
Ethnic - Not Hisp or Latino	23	25	0	48
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	26	27	0	53
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	10	13	0	23
White	15	14	0	29
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	26	27	0	53
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	3	2	0	5
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	3	2	0	5

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	1	0	1
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	2	0	2
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	2	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	2	0	2
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	1	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	1	0	1

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	3	2	0	5
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	2	0	5
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	2	2	0	4
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	2	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 16

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	5	6	1	12
Ethnic - Not Hisp or Latino	105	90	0	195
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	110	96	0	207
Amer Indian/Alaska	0	0	0	0
Asia	3	0	0	3
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	51	55	0	106
White	55	41	1	97
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	110	96	1	207
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	5	6	1	12
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	5	6	1	12

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	1	2	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	2	0	4
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	1	0	2
White	1	1	0	2
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	2	0	4
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the GDB Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	18	24	1	43
Ethnic - Not Hisp or Latino	48	41	0	89
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	66	65	0	132
Amer Indian/Alaska	0	0	0	0
Asia	3	2	1	6
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	30	25	0	55
White	33	37	0	70
More than One	0	1	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	66	65	1	132
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	1	1
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	1	0	1
Hispanic: White	18	23	0	41
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	18	24	1	43

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Inclusion Enrollment Report for the Support Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	6	0	7
Ethnic - Not Hisp or Latino	6	6	0	12
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	7	12	0	19
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	4	4	0	8
White	3	8	0	11
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	7	12	0	19
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	6	0	7
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	6	0	7

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Inclusion Enrollment Report for the Follow-up Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	12	11	0	23
Ethnic - Not Hisp or Latino	28	16	0	44
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	40	27	0	67
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	16	10	0	26
White	23	17	0	40
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	40	27	0	67
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	12	11	0	23
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	12	11	0	23

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	5	4	0	9
Ethnic - Not Hisp or Latino	1	1	0	2
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	6	5	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	6	4	0	10
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	6	5	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	5	4	0	9
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	5	4	0	9

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Hypothermia Extended Follow-up Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	5	4	0	9
Ethnic - Not Hisp or Latino	1	1	0	2
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	6	5	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	6	4	0	10
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	6	5	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	5	4	0	9
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	5	4	0	9

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the Support Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	6	0	7
Ethnic - Not Hisp or Latino	6	6	0	12
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	7	12	0	19
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	4	4	0	8
White	3	8	0	11
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	7	12	0	19
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	6	0	7
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	6	0	7

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Inclusion Enrollment Report for the Follow-up Study for Center 18

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	12	11	0	23
Ethnic - Not Hisp or Latino	28	16	0	44
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	40	27	0	67
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	16	10	0	26
White	23	17	0	40
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	40	27	0	67
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	12	11	0	23
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	12	11	0	23

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	3	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	3	0	3
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	2	0	2
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	3	0	3
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Support Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	3	7	0	10
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	7	0	10
Amer Indian/Alaska	0	1	0	1
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	4	0	5
White	2	2	0	4
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	7	0	10
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Report created on 01/21/09

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	0	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	0	0	0	0
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	0	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	0	0	3
Ethnic - Not Hisp or Latino	32	44	0	76
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	35	44	0	79
Amer Indian/Alaska	1	1	0	2
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	15	28	0	43
White	18	14	0	32
More than One	0	0	0	0
Unknown or Not Reported	1	0	0	1
Racial Categories: Total of all	35	44	0	79
Hispanic: Amer Indian/Alaska	1	0	0	1
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	0	0	1
Hispanic: Racial Categories: Total of al	3	0	0	3

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Inclusion Enrollment Report for the Follow-up Study for Center 19

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	5	0	8
Ethnic - Not Hisp or Latino	25	21	1	47
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	28	26	0	55
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	1	0	0	1
Black or African Amer	17	14	0	31
White	9	12	1	22
More than One	0	0	0	0
Unknown or Not Reported	1	0	0	1
Racial Categories: Total of all	28	26	1	55
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	0	0	1
Hispanic: White	1	5	0	6
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	1	0	0	1
Hispanic: Racial Categories: Total of al	3	5	0	8

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Inclusion Enrollment Report for the Follow-up Study for Center 22

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	7	0	13
Ethnic - Not Hisp or Latino	4	4	0	8
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	10	11	0	21
Amer Indian/Alaska	0	0	0	0
Asia	2	1	0	3
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	8	10	0	18
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	10	11	0	21
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	1	0	0	1
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	5	7	0	12
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	7	0	13

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Inclusion Enrollment Report for the Support Study for Center 22

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	2	0	3
Ethnic - Not Hisp or Latino	0	3	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	5	0	6
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	1	5	0	6
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	5	0	6
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	2	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	2	0	3

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 23

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	0	0	1
Ethnic - Not Hisp or Latino	2	2	0	4
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	2	0	5
Amer Indian/Alaska	0	0	0	0
Asia	1	0	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	1	2	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	2	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	0	0	1
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	0	0	1

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Inclusion Enrollment Report for the Support Study for Center 23

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	6	0	8
Ethnic - Not Hisp or Latino	1	2	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	3	8	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	2	8	0	10
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	3	8	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	0	0	1
Hispanic: White	1	6	0	7
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	6	0	8

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 23

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	0	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	1	0	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	0	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 23

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	17	0	23
Ethnic - Not Hisp or Latino	15	24	0	39
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	21	41	0	62
Amer Indian/Alaska	0	0	0	0
Asia	3	2	0	5
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	4	3	0	7
White	14	36	0	50
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	21	41	0	62
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	1	0	1
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	2	1	0	3
Hispanic: White	4	15	0	19
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	17	0	23

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Inclusion Enrollment Report for the Follow-up Study for Center 23

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	6	8	0	14
Ethnic - Not Hisp or Latino	8	10	0	18
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	14	18	0	32
Amer Indian/Alaska	0	0	0	0
Asia	1	1	0	2
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	4	0	7
White	10	13	0	23
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	14	18	0	32
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	0	0	1
Hispanic: White	5	8	0	13
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	6	8	0	14

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	3	0	3
Ethnic - Not Hisp or Latino	4	3	0	7
Ethnic - Unknown	1	0	0	1
Ethnicity: Total of All Subjects	5	6	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	3	6	0	9
More than One	1	0	0	1
Unknown or Not Reported	1	0	0	1
Racial Categories: Total of all	5	6	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	3	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	3	0	3

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Inclusion Enrollment Report for the Support Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	4	7	0	11
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	7	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	2	0	3
White	3	4	0	7
More than One	0	1	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	7	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	1	4	0	5
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	4	0	5
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	1	3	0	4
More than One	0	1	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	4	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the Late Hypothermia Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	0	1	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	0	1	0	1
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	0	1	0	1
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	0	1	0	1
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Inclusion Enrollment Report for the GDB Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	3	0	6
Ethnic - Not Hisp or Latino	22	23	1	46
Ethnic - Unknown	2	1	0	3
Ethnicity: Total of All Subjects	27	27	0	55
Amer Indian/Alaska	0	0	0	0
Asia	2	0	0	2
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	3	7	0	10
White	19	17	1	37
More than One	1	2	0	3
Unknown or Not Reported	2	1	0	3
Racial Categories: Total of all	27	27	1	55
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	1	0	1
Hispanic: White	3	2	0	5
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	3	3	0	6

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Inclusion Enrollment Report for the Follow-up Study for Center 24

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	1	0	2
Ethnic - Not Hisp or Latino	7	7	0	14
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	8	8	0	16
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	7	7	0	14
More than One	0	1	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	8	8	0	16
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	1	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	1	0	2

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Inclusion Enrollment Report for the GDB Study for Center 25

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	24	18	0	42
Ethnic - Not Hisp or Latino	50	62	0	112
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	74	80	0	154
Amer Indian/Alaska	1	0	0	1
Asia	4	3	0	7
Hawaiian or Other Pacific	1	0	0	1
Black or African Amer	4	6	0	10
White	60	68	0	128
More than One	1	0	0	1
Unknown or Not Reported	3	3	0	6
Racial Categories: Total of all	74	80	0	154
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	2	1	0	3
Hispanic: White	20	14	0	34
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	2	3	0	5
Hispanic: Racial Categories: Total of al	24	18	0	42

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 25

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	3	0	6
Ethnic - Not Hisp or Latino	3	10	0	13
Ethnic - Unknown	0	1	0	1
Ethnicity: Total of All Subjects	6	14	0	20
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	1	0	1
Black or African Amer	1	3	0	4
White	3	8	0	11
More than One	1	1	0	2
Unknown or Not Reported	1	1	0	2
Racial Categories: Total of all	6	14	0	20
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	1	2	0	3
Hispanic: White	2	1	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	3	3	0	6

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Follow-up Study for Center 25

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	2	0	0	2
Ethnic - Not Hisp or Latino	6	8	0	14
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	8	8	0	16
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	7	8	0	15
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	8	8	0	16
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	2	0	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	2	0	0	2

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
Report created on 01/21/09

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Inclusion Enrollment Report for the Support Study for Center 25

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	3	0	0	3
Ethnic - Not Hisp or Latino	6	11	0	17
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	9	11	0	20
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	9	10	0	19
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	9	11	0	20
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	3	0	0	3
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	3	0	0	3

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Inclusion Enrollment Report for the Physiologic Definition Study for Center 25

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	0	0	0
Ethnic - Not Hisp or Latino	4	7	0	11
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	4	7	0	11
Amer Indian/Alaska	0	0	0	0
Asia	0	1	0	1
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	1	0	1
White	3	5	0	8
More than One	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	4	7	0	11
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	0	0	0
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	0	0	0

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Report created on 01/21/09

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Inclusion Enrollment Report for the Early Onset Sepsis Study for Center 26

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	1	7	0	8
Ethnic - Not Hisp or Latino	1	0	0	1
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	2	7	0	9
Amer Indian/Alaska	0	0	0	0
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	0	0	0	0
White	2	7	0	9
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	2	7	0	9
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	1	7	0	8
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	1	7	0	8

Total includes patients entered into study or status obtained on and between 01/01/08 and 12/31/08
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Inclusion Enrollment Report for the Follow-up Study for Center 26

Categories	Females	Males	Unknown	total
Ethnic - Hisp or Latino	0	2	0	2
Ethnic - Not Hisp or Latino	1	2	0	3
Ethnic - Unknown	0	0	0	0
Ethnicity: Total of All Subjects	1	4	0	5
Amer Indian/Alaska	0	1	0	1
Asia	0	0	0	0
Hawaiian or Other Pacific	0	0	0	0
Black or African Amer	1	0	0	1
White	0	3	0	3
More than One	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of all	1	4	0	5
Hispanic: Amer Indian/Alaska	0	0	0	0
Hispanic: Asia	0	0	0	0
Hispanic: Hawaiian or Other Pacific	0	0	0	0
Hispanic: Black or African Amer	0	0	0	0
Hispanic: White	0	2	0	2
Hispanic: More than One	0	0	0	0
Hispanic: Unknown or Not Reported	0	0	0	0
Hispanic: Racial Categories: Total of al	0	2	0	2

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Huitema, Carolyn Petrie
Subject: updated Duke site report
Date: Friday, October 02, 2009 6:53:31 PM
Attachments: Duke Site Visit 20090929_kzbvs20091001.doc

HI,
Here is the updated Duke site visit report draft.
Thanks,
Kris

Kris Zaterka-Baxter
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NICHD NRN Duke Site Visit
September 29, 2009

NICHD: Dr. Rosemay Higgins
Data Coordinating Center: Kristin Zaterka-Baxter, Carolyn Huitema
Duke University: Drs. Ronald Goldberg, Michael Cotten, Kimberly Fisher

Minutes

Regulatory Review

New to the review process at Duke is the Site Base Research Unit (SBRU) related to billing and budget. The intent is to insure that a billing grid is developed and used for billing tracking with respect to research and clinical costs covered by insurance. Standard of care medical items and procedures must also be included in this billing grid. The billing grid with color coding for a protocol must be done before the protocol can be submitted for departmental and IRB review. The Duke NRN group will have to go back and develop a billing grid for each active study as the IRB yearly approvals come up. The SBRU does not charge for their review but the amount of time unit or research staff spends preparing for this review is substantial. Time includes finding CPT codes and working with the PRMO (pricing oversight office).

Once the SBRU approves the protocol then the NRN staff at Duke may submit the protocol through the following series of review:

1) Departmental Review (Dr. Cotten serves on this board). This can take a turnaround time of 1-4 weeks
2) Department Chair to assign pediatric risk level. Turnaround time is 1-3 days.
3) IRB medical writer reviews application with a turnaround of 1-2 weeks. They mainly look at the wording of the consent form.
4) Then, the protocol moves to IRB review.

Currently there are 8 IRBs at Duke, 4 chairs and 8 vice chairs. If assigned a low risk, the protocol is usually expedited. If higher risk, the protocol goes to Full Board. A primary reviewer is assigned and usually approves the protocol with minor changes. The water mark consent does not get released by Office of Research Assistants (ORA) until the SBRU grid is approved after any final additional changes. This appears to be a burdensome process. The Duke NRN site IRB approvals take longer than many to most NRN site IRB approvals.

Dr. Fisher usually takes care of the IRB and SBRU process and can call on others to help as needed.

Renewal announcements are sent 2-3 months before the deadline however, the Duke NRN staff tracks the renewals. They can only submit a renewal 60-45 days from deadline.

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Duke has a current indirect rate of 57%. This may require renegotiation to compensate for the extensive reviews. A new Vice Dean of Clinical Research has just been appointed.

Dr. Fisher suggested that UNC-CH submit at the same time to prevent a gap in the approvals. UNC-CH usually receives IRB approval prior to Duke. The UNC site cannot recruit until the Duke primary NRN site has IRB approval as the data is entered through the NRN computer at Duke.
Current status of upcoming trials:

- INS2 has gone through departmental review. Now that the doses are assigned, it is moving to Full Board review
- NEST is in the SBRU process

Other Study Sites

Durham Regional Hospital (DRH)
The Duke NRN staff has access to the discharge summaries at DRH from which GDB data are collected. For the SUPPORT Trail, the Duke site decided not to recruit at DRH due to the issue of keeping track of the Masimo study oximeters. It was decided by the Duke staff to try not to transfer children in the SUPPORT Trial on study oximeters to DRH since it would be very difficult to manage them on the study and rarely do they transfer children on oxygen to DRH. and they tended to hold onto infants who were enrolled in SUPPORT. Infants born at DRH were not enrolled in SUPPORT though mothers at risk for extreme preterm deliveries were usually transferred to Duke. but they did try to move mothers who might delivery eligible infants. The Duke NRN staff were unsure if they had permission to collect SUPPORT data elements from DRH. The Duke NRN staff were unsure if they needed DRH IRB approval or if DRH is part of the Duke University Healthcare System and therefore one approval from the Duke IRB is needed. Dr. Cotton learned that DRH does accept Duke IRB approval but that DRH must administratively approve the study. DRH no longer has a separate IRB. Dr. Cotton submitted and amendment to the Duke Support Trial submission to include DRH. Since DRH is listed in the Duke NRN grant application as a population available for clinical trials, NICHD requests that the Duke site insure that they can collect research data from DRH.

Comment [k1]: This sounds like they are keeping kids in house longer than medically necessary because they are enrolled in a research study; would delete this text

Comment [k2]: This too; sounds like they are transferring kids to Duke just because of the study; not because all high risk pregnancies get transferred to Duke; would also delete

There was confusion regarding the determination of status for Support study patient transferred to DRH due to the uncertainty of IRB approval status at that site., Seven study infants who were transferred to DRH were coded with a status of transferred in the Support trial data and coded as discharged to home in the GDB data (because these infants were discharged to home from DRH). Additionally, if the infant was transferred prior to 36 weeks PMA to DRH, the Support Trial data collection was halted at time of transfer. Ultimately, it was determined that Duke would gain the regulatory and administrative approval from Duke and DHR respectively in order to collect and amend the necessary research data.

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Alamance Regional Medical Center:
Alamance has a low census and separate IRB. They currently do not participate in the NRN studies. The census may increase since they are working with public health clinics. If this is the case; Duke will recruit infants to study with local IRB approval. If the census does not improve, a modification of the Duke NRN grant application listing Alamance Regional as part of the population base for research studies may be requested.

Comment [k3]: Rose; not sure this is correct about the grant app)

Duke Health-Raleigh:
This site has closed since the grant application was filed.

Moore Regional Hospital:
Clarification is requested regarding whether Moore Regional is a participating Duke site for the recruitment and enrollment of NRN study infants.

University of North Carolina at Chapel Hill (UNC-CH)
This site was added in November 2008. Since, they have obtained IRB approval to conduct GDB data collection and 2 NRN research studies. Enrollment and data collection seem to be going well (Duke has been asked to send all UNC IRB approvals and approved informed consents where applicable to RTI fro their records). Since UNC staffs their research office separately from it was suggested that Duke, as the primary site, plan to monitor data collected by UNC with source documents as a matter of QA/QC.

Study Consent
A consent/data entry issue was discussed regarding a case where parent(s) gave consent for SUPPORT but declined GDB. The parent(s) were re-approached for GDB consent during their infants 18M follow up visit. Consent was granted at that time however the Support data was held until GDB approval was granted. This resulted in a SUPPORT enrollment post completion of study recruitment.

Guidelines should be put place for research studies requiring GDB data a part of the interventional study to insure all research data are obtainable and in an appropriate timeframe. This is a site issue and the site needs to insure that patients enrolled in trials will have the necessary research data available for collection.

Embedding the GBD consent to collect data into the clinical research trial consent was proposed as a possible solution. Drs. Cotton and Goldberg will investigate this possibility however have indicated that in the past, their IRB was very much against the approach of 'bundling' studies into one consent. The possibility of complete de-identification of GDB study data was discussed as a possible avenue for requesting waiver of consent for GDB, however, Duke regulatory guidelines indicated that any link to a study subjects identification, including study logs kept in house, render that subject as identifiable and thus requires the potential subject's consent to participate (parental consent).

Performance
Dr. Higgins presented the most recent NRN snapshot of performance (June 2009) at all NRN centers. This sheet will be distributed to the study section for peer review when the

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network is reviewed in fall 2010. Duke was falling behind at 68% ROP outcome for SUPPORT at end of June.

To resolve this issue Duke recently developed a plan to obtain a copy of all in-house and out-patient return visit ROP exam reports and maintain a copy of these reports in the research files. Until recently there was significant difficulty in obtaining a copy of the ophthalmology report from the Duke Eye Center. When this was ultimately brought to Dr. Goldberg's attention in the last month or so, a phone call from Dr. Goldberg improved this process. When the study infants are discharged, Duke NRN staff calls the outside ophthalmologist to get a copy of the exam (with an acceptable form of authorization, i.e., signed medical release form or copy on the study informed consent)

There were11 patients in the NRN DMS as of 9/25/09 that did not have final outcome for ROP. This was corrected on site at the time of this review.

Meetings

There are two weekly meetings. The first meeting is a larger pediatric research meeting with all research staff including the Duke NRN staff and other investigators. The second meeting includes NRN research nurses and data entry and is headed by Dr. Fisher.

Going forward, NICHD requests that a weekly meeting be held with Drs. Cotton, Goldberg, Fisher, NRN research nurses and staff, follow up and data entry staff. This will facilitate communication and hopefully prevent delays in issues being addressed such as delays with the eye exams that were previously encountered at the site. Duke has taken steps in planning for these meetings.

Protocol Communication

The protocol is received by NRN (passed concept stage and initial protocol review). The process initial review process begins at Duke with protocol review by PI, Alt PI and FU PI as well as select faculty for specific expertise/interest for input. The study PI compiles responses from faculty and hopefully identifies a study champion among faculty with interest/expertise. After, the protocol is more generally presented to faculty, fellow, NNPs. NRN staff also begins IRB preparation with consideration of protocol development timeline within the NRN. Once Network approved, the NRN staff work on the regulatory documents for Departmental review. NRN staff responds to Department recommendations and once approved at this level, ultimately submit for IRB/IRB chair review. Once final IRB approval has been granted, NRN staff plan in-service(s) for the NICU clinical team.

Staffing/Hiring

The Human Resources (HR) department at Duke seems to be an obstacle in hiring appropriate staff in a timely manner. There is a need for several staff (research nurses/study coordinators) in the NICU research department and there are several positions posted which are seemingly difficult, at best, to fill. The salary for these positions is set by the Duke HR department, regardless of the available NIH grant funding for NICHD projects. The salary listed on the grant is not the salary used in the

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Duke system to advertise the job. A lower salary is used, perhaps limiting the applicant pool and generating less qualified applicants. It is not clear to NICHD how guidelines are used to set the salaries if a key personnel position at a requested salary level has been listed in the grant application. Once the candidate is identified, the process for a job offer takes approximately 1 month. Dr. Goldberg stated that qualified candidates were lost because they took other positions which were offered in a timelier manner. Given the essential and critical role of the research coordinator at the NRN sites, efficient recruitment for this position is necessary. The current coordinator, Gloria Siaw, began work in mid-March 2009, the previous coordinator resigned with an effective date of December 31 leaving the research coordinator position vacant for over 2 months.

Enrollment

NRN research coordinators and nurses as well as neonatal fellows and faculty participate in enrollment of infants to study. Dr. Cotten, Goldberg, Goldstein and Fisher primarily discuss the NRN studies with patent(s) of potential infants and seek written consent. Dr. Cotten is primarily responsible for SUPPORT and the 6-24 Hour Hypothermia consent process and Dr. Goldstein facilitates the Preemie aEEG consenting process. Dr. Goldberg assists where necessary.

In addition to the NRN studies, there are about 42 active trials (industry and grant funded). The only foreseeable conflict for enrollment is with an on-going anti-fungal medication study (Fluconozole) with the upcoming Inositol Multi-dose Pk study and they are both conducted under IND.

Data Collection

NRN Staff may need to approach parent(s) for consent several times if necessary prior to consent being granted. Dr Goldberg or Cotton may also approach parent(s) for further discussion of study participation. Follow Up consent is now typically obtained just before discharge. GDB data is collected in real time on Monday, Wednesday and Fridays primarily by the research coordinator and research nurse with assistance of the clinical research director where necessary. For interventional studies, data is collected daily. There are recent operating procedures in place that allow source documentation to be readily available in the patient research record.

Forms are completed and sent to the Data Entry person (presently Charles Vajdl) for keying data into the NRN DMS computer located at his desk. If he has data questions, he flags the forms and asks the Research Coordinator (presently Gloria Siaw), the Research Nurse (presently Stephanie Crosby) or the Director of Clinical Research (presently Dr. Kim Fischer) for assistance. The later three staff also assist in data entry when required. All NRN staff have been trained and certified to enter data in the NRN DMS to ensure cross coverage.

Currently there are no formal quality checks on UNC-CH data. Duke and UNC research staff meet on a monthly and this would provide good forum to review data and research processes. Regulatory information is kept in a single location at UNC-CH. All IRB

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approvals and approved consent forms must be sent to RTI for both Duke as well as UNC.

Procedure for Queries, Edits and Data Quality

The data entry person prints off edits and works with the research coordinator and director to resolve them. Duke had the highest rate of missing forms for the Support trial (just under 50% of the total forms outstanding cross NRN centers) as of September 3, 2009. A written plan for procedures and process for dealing with and resolving queries and edits is required from Duke.

Dr. Higgins sends missing primary outcome data to all sites on a monthly (or more frequent interval depending on the state of a trial) basis to all NRN sites. Drs. Goldberg, Cotton, Fischer, and Ms. Siaw receive the list. If there are follow up outcomes, Dr. Goldstein is also notified. Dr. Goldberg forwards to Drs. Cotten and Fisher and Ms. Siaw. It is not clear who has the responsibility for resolving the queries and edits; staff need to be identified and responsibilities outlined in detail for resolution of missing forms, batched edits and queried. Dr. Fisher is now in the process of resolving outstanding in light of several staffing issues.

Cross checks with GDB and SUPPORT have been generated by RTI. It is of great concern that 5 infants in SUPPORT had grade III or IV IVH reported on SUPP09, but no IVH on the NG03 status form. Both forms are using the same definitions for IVH. The data need to be consistent on individual infants and the site is requested to insure consistency and accurate data collection. A plan for cross checking data should be put into place at the site.

Action items requiring a response to NICHD by October 15, 2009:

1. The collection of research data at DRH needs to be addressed and resolved so that source document can be obtained on infants in observational studies and trials can have complete data in the DMS.
2. A written plan for the process and resolution of edits and queries needs to be formulated and instituted at the Duke site detailing responsibility for staff completing the entry to RTI. This must be sent to NICHD.
    a. All SUPPORT missing forms, batch edits, queries and action items listed below must be resolved immediately.
3. Duke is required to have all SUPPORT study primary outcomes for all 64 cases verified and the Primary Outcomes Report signed by Dr. Goldberg and/or Dr. Cotton to ensure the integrity of the data.
    a. In addition, it is imperative that all data and neuro-images be sent to RTI immediately for the Support Neurodevelopmental Secondary Study. There are currently 2 infants with missing MRI images (72101; 72051)
4. A Weekly meeting for the NRN research staff (PI, alternate PI, Follow Up PI, clinical research director, research coordinator, research staff and data entry staff) is strongly encouraged to facilitate communication, resolution of current

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outstanding data, and ongoing protocol updates as well as other items relevant to NRN research.

5. The establishment of a communication plan for the Rochester site conducting the SUPPORT Secondary Breathing Outcomes interviews is requested. Ms. Zaterka-Baxter will Assist Dr. Fisher and send the necessary information to establish this process. THE Breathing Outcomes FU windows for all patients are posted to the private NRN gateway.

Recommendations

1. The inclusion of frequent transfer sites (NHMH; Rex Hospital) in NRN study informed consented to allow collection of required study data was suggested but it is understood that is the prevue of the Duke IRB.
2. The Duke site appears to have an arduous IRB process as well as challenges with hiring and retaining coordinators for the NRN activities. It is suggested that the PI work with the appropriate individuals at the institution to facilitate these two areas that have been a bit challenging for the NRN at Duke.

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Full Case Review

(b) (6)

Support Trial Outcome Data:

ROP outcome data reviewed against source documents (ophthalmologic reports);

Action Items:

None

BPD outcome data reviewed against source documents (medical records)

Action Items:

None

Follow up #1271

Action Items:

1. Follow Up Consent was not available in the study folder; please copy and submit to RTI. Noted was a signed North Carolina Infant Toddler Authorization to disclose health information.
2. No CRFs were included in the study folder though NF09A was verified using remote data; please update study files

(b) (6)

Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);

Action Items:

1. Amend and verify data for exam date (b) (6); per source documentation, it does not appear the infant had threshold disease in the left eye.
2. Per chart review on 09/01/09; please verify and enter exams for the following data in the DMS:
   (b) (6)

BPD outcome data reviewed against source documents (medical records)

Action Items:

1. Post Duke IRB approval to collect pulmonary data at DRH; please enter all data to 36 weeks /status on the NG07 and Supp11

Follow up #1278

Action Items:

1. Not all CRFs were included in the study folder (NF01 and NF09A were reviewed); please update study files

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(b) (6)
Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:
1. Final ROP status missing; resolve or amend data

BPD outcome data reviewed against source documents (medical records)
Action Items:
1. Data inconsistent with source documentation in the supp11 for date (b) (6) @ 0600 time point – should be CPAP (4) not CV (2). Please amend data

Follow up # 1342
Action Items:
1. Follow Up Consent was not available in the study folder; please copy and submit to RTI
2. No CRFs were included in the study folder though NF09A was verified using remote data; please update study files

(b) (6)
Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:
None

BPD outcome data reviewed against source documents (medical records)
Action Items:
None

Follow up #1455
Action Items:
1. Follow Up Consent was not available in the study folder; please copy and submit to RTI
2. No CRFs were included in the study folder though NF09A was verified using remote data; please update study files
3. NF09A: one transcription error. Receptive Communication scaled score recorded as 12 in DMS but listed as 13 on the source document; please amend data on form, in DMS and transmit.

(b) (6)
Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:
1. Source documents inconsistent with data entered to DMS; no stage 4 disease in the right eye on exam date (b) (6) and (b) (6) ; please amend data.

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2. Source documents inconsistent with data entered to DMS; no stage 3 disease but GBD data NG03 Q.A.1.a.1 is coded as YES; please amend data

BPD outcome data reviewed against source documents (medical records)
Action Items:
None

Follow up #1380
Action Items:
None

(b) (6)
Support Trial Outcome Data
ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:
None

BPD outcome data reviewed against source documents (medical records)
Action Items:
None

Follow up #1419
Action Items:
1. Follow Up Consent was not available in the study folder; please copy and submit to RTI
2. No CRFs were included in the study folder though NF09A was verified using remote data; please update study files

(b) (6)
Support Trial Outcome Data
ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:
1. Source documentation is inconsistent with data entered in DMS; dates of exams appear to be inconsistent with reported findings ((b) (6) {fully vascularized}); please review and amend data. Please copy all eye exam reports and send to RTI once data are amended for further review.

BPD outcome data reviewed against source documents (medical records)
Action Items:
1. No action items but noted that infant transferred to REX at 33 wks PCA (b) (6) on RA at 36wks.

Follow up # 1438
Action Items:
1. None; follow up window not yet open

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(b) (6)

Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);

Action Items:

1. Source documentation is inconsistent with data entered in DMS;
2. No SUPP09 in DMS; please key and transmit data
3. SUPP10-missing eye exams
    a. Missing exam in DMS on (b) (6) source documents indicate infant had Left eye-surgery on this date; please amend data
    b. No source document for ROP exam on (b) (6); DMS indicated data for right eye-surgery on this date; please verify
    c. Source documents indicate infant has plus disease; documented on GDB NG03 Q.H.1.a.1 and NO; please verify and amend data. Please send missing eye exam reports to RTI for further review

BPD outcome data reviewed against source documents (medical records)

Action Items:

None

Follow up # (none assigned at this time); Follow up window not open

Action Items:

1. Please verify if infant was consented at discharge; if so, provide a copy of the informed consent to RTI

(b) (6)

Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);

Action Items:

1. Source documentation is inconsistent with data entered in DMS; the last to ROP exam reports are not entered in the DSM; please update system and send reports to RTI for further review.

BPD outcome data reviewed against source documents (medical records)

Action Items:

1. Infant transferred to DRH prior to 36 weeks; please amend correct all missing data on Supp11 and NG07 with local IRB approval and submit data to RTI.

Follow Up #1471

Action Item:

1. Follow Up Consent was not available in the study folder; please copy and submit to RTI
2. No CRFs were included in the study folder though NF09A was verified using remote data; please update study files

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(b) (6)
Physician removed infant from study due to unblinding of the oximetry arm; the infant was not withdrawn as documented in the data. The Supp06 PD from will be amended and all data with be entered in DMS with approved consent from parents.

Support Trial Outcome Data

ROP outcome data reviewed against source documents (ophthalmologic reports);
Action Items:

1. Source documentation inconsistent with entered data; final ROP outcomes of laser surgery in both eyes documented per source on (b) (6) but reported in DMS as occurring on (b) (6); please amend data

BPD outcome data reviewed against source documents (medical records)
Action Items:

1. In light of resolution of infants status (not withdrawn), please update all data and transmit to RTI. SUPP11 need to complete forms

Follow up # (none assigned at this time); Follow up window not open
Action Item:

2. Please verify if infant was consented at discharge; if so, provide a copy of the informed consent to RTI

BPD Phys Def vs. BPD 02 Cases

(b) (6)
Findings and Action items:

1. NG07 v 1.1.06 question 8, 36 wk snapshot = YES (NC). SUPP11 is coded as NC all day at 36 wks but PHY01 is coded as nasal CPAP YES and did not answer NC question. Question 8 circled as YES at 36 wk snapshot (form in file, yes to vent, CPAP or NC and RA). Please verify data and verify whether infant was eligible for the physiologic challenge for BPD.
2. Question B.4 on the PHY01 is coded as YES for vent or CPAP; if data are correct above on the NG07, amend data in Q.B.4 and B.7 and transmit to RTI.

(b)
Findings and Action items:

1. Refer to above case. Fixed in DMS on-site

(b)
Findings and Action items:

1. Noted that the 36 week date on the Supp11 was incorrect; this is noted for the sites use, this data is not keyed. No action required.

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(b) (6)
Findings and Action items:
1. Verfiy oxygen use at transfer. SUPP11 (coded as using oxygen) on day of transfer which does not match NG07 at Status (RA at status).

(b) (6)
Findings and Action items:
NG07 36 wk BPD data verified vent or CPAP and RA. No action required

(b) (6)
Findings and Action items:
Refer to above.

Transferred Cases

NG07 data were deleted because Duke changed status from discharged to home (form DRH) to transfer (from Duke). It was unclear whether DRH was a participating ancillary site of Duke and under appropriate IRB review. Duke will clarify whether DRH fall under the Duke University Health System regulatory prevue. With IRB approval, Duke will amend the NG03, NG07, Supp09, Supp10 and Supp11 data (where applicable) for the infants listed below.

Additional Findings upon brief review requiring attention:

(b) (6) No threshold disease per source documents but coded in the DMS as such; please verify
(b) (6) NC v. CPAP at36wk; please verify
(b) (6) 11/3/09 oxygen=4, updated and fixed in DMS on 9/27/09
(b) (6) No additional comments
(b) (6) RA vs oxygen at 36 weeks; please verify data
(b) (6) Transferred at 33 weeks to Rex Hospital on oxygen however 36 week data per NG07 is coded as on RA; please verify data and amend.
(b) (6) Incomplete Supp10 data; right eye exam on (b) (6) is not entered in the DMS
(b) (6) No additional comments

Other Items

New Queries generated 9/29/2009 and should be completed immediately

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu; gloria.siaw@duke.edu; goldb008@mc.duke.edu; "Ricki F Goldstein"; "Gantz, Marie"
Subject: Re: SUPPORT!!!!!
Date: Friday, October 02, 2009 4:43:06 PM

Rose
I have completed the queries listed in the the text as follows

(b) (6) - I spoke to Kris about this and we had it keyed incorrectly so it has been corrected and transmitted tonight
(b) (6) are both subjects that were transferred to (b) (6) but the 36 week info has now been re-keyed and has been transmitted

The attachment titled "Infants Missing ROP Outcomes at Center 19" with 5 infants listed has been completed and transmitted. I spoke with Kris aobut this and had to make one other correction which has been done.

I will work on the BPD attachment tomorrow.

Thanks for all your help!
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970(b) (6)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/02/2009 03:21 PM

To "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "'Ricki F Goldstein'" <golds005@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "gloria.siaw@duke.edu" <gloria.siaw@duke.edu>
cc "'Gantz, Marie'" <mgantz@rti.org>
Subject SUPPORT!!!!!

Hi,
Attached are ROP and BPD queries. We are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study. Many of these are previously "excused," but we still have no firm ROP

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outcome on these infants. If you have any way of determining ROP outcome, please let us know. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
CENTER	NETWORK	BPD_message
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Bethesda, MD 20892
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higginsr@mail.nih.gov

[attachment "SUPPORT infants missing ROP - Center 19 02OCT09.rtf" deleted by Kimberley A Fisher/Pediatrics/mc/Duke] [attachment "SUPPORT BPD queries Center 19 (09-30-09).rtf" deleted by Kimberley A Fisher/Pediatrics/mc/Duke]

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From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg; Ricki F Goldstein; Kimberley A Fisher; Gloria Siaw
Cc: "Gantz, Marie"
Subject: Re: SUPPORT!!!!
Date: Friday, October 02, 2009 3:54:22 PM

Hi Rose

Is 97 the whole network or just duke (thought we had 64)?

From: "Higgins, Rosemary (NIH/NICHD) [E]" [higginsr@mail.nih.gov]
Sent: 10/02/2009 03:20 PM AST
To: Ronald Goldberg; Ricki Goldstein; Kimberley Fisher; Michael Cotten; Gloria Siaw
Cc: "Gantz, Marie" <mgantz@rti.org>
Subject: SUPPORT!!!!!

Hi,
Attached are ROP and BPD queries. We are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study. Many of these are previously "excused," but we still have no firm ROP outcome on these infants. If you have any way of determining ROP outcome, please let us know. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	SUPP10 Q:Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

CENTER	NETWORK	BPD_message
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19		Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.

Rosemary D. Higgins, MD
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil; Wally Carlo; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates
Date: Friday, October 02, 2009 3:42:32 PM

Rose and I were talking earlier and thought that we should also send out the ROP queries (about data inconsistencies) we had discussed at the Rockville meeting and a few others Rose has suggested (for example, comparing surgery on the NG03 and SUPP10). I will get those together ASAP to send to the centers.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 02, 2009 3:36 PM
To: Gantz, Marie
Cc: Finer, Neil; Wally Carlo; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates

I sent them all out – lets hope we get quick responses.
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 02, 2009 2:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil; Wally Carlo; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are the following:

1) A zipped file containing documents for each center with unresolved BPD queries. (Centers without a document have no outstanding queries.) Queries that have potential to change the BPD outcomes are highlighted in yellow. Other queries address missing forms (like the SUPP11) and other data inconsistencies that will not necessarily affect whether the infant is classified as having BPD or not.
2) A zipped file containing documents for each center with infants who are missing final ROP status. (Centers without a document have no outstanding ROP outcomes.) Note that these documents list all infants without a ROP final outcome, including those whom the centers have coded on the SUPP10 as having the acute ROP outcome missing at 55 weeks PMA and/or having not obtained final ROP status at the 18 month FU visit.
3) An Excel file with the usual missing data reminders for ROP, BPD and FU.

We are currently missing ROP on 104 infants: 4 have been withdrawn from the study, 1 with vessels in zone 1 at last exam, 47 with vessels in zone 2 at last exam, and 52 with vessels in zone 3 at last exam. However, the 104 also includes three infants who were found at follow-up to have died after discharge, two at about 7 months old, and one at about a year old. Thus, we are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study.

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Marie

Marie Gantz, Ph.D.
Research Statistician
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828-254-6255

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From: Adams-Chapman, Ira
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Cc: "Gantz, Marie"
Subject: RE: SUPPORT!!!
Date: Friday, October 02, 2009 3:38:35 PM

Rose - we are working to see if we can track down any othe outstanding ROP exams from our site. Will have additional staff with time to dedicate to finding them next week. We will keep you posted.
Thanks,
Ira

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, October 02, 2009 3:08 PM
To: Adams-Chapman, Ira; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Cc: 'Gantz, Marie'
Subject: SUPPORT!!!

Hi,

Attached are ROP and BPD queries. We are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study. Many of these are previously "excused," but we still have no firm ROP outcome on these infants. If you have any way of determining ROP outcome, please let us know. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "dale_phelps@urmc.rochester.edu"; "Reubens, Linda"; "Jensen, Rosemary"
Cc: "Gantz, Marie"
Subject: SUPPORT!!!
Date: Friday, October 02, 2009 3:22:00 PM
Attachments: SUPPORT BPD queries Center 21 (09-30-09).rtf
Importance: High

Hi,

Attached are BPD queries. The data base will be LOCKED following data entry on OCTOBER 20, 2009.

Please attend to these asap. Thanks for all the effort!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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higginsr@mail.nih.gov

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SUPPORT BPD Queries for Center 21-University of Rochester

Center ID number=21=University of Rochester Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01y1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01y1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
Y	Y	N	Y	.	O2	O2	O2	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC
	.	.	.	.	.	.	.	.	.

NG07 @status O2 by NC	Query 1	Query 2	Query resolution: Center notes
.	Number of days on vent/CPAP @36wks =DOL @36wks per NG07 but infant not on vent/CPAP @36wks per NG07 and/or SUPP11.		

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT missing data updates
Date: Friday, October 02, 2009 2:57:34 PM

Hi Rose, I know we just spoke on the phone, but here is the response I was writing. There was one other question I meant to ask you, which was whether you are alright with Neil's response that we will use the strict definition of supplemental oxygen for the "traditional" BPD outcome (leaving kids on room air by vent or CPAP to be classified as BPD=No)?

RESPONSE TO EMAIL BELOW:
Right now all infants but one currently have a classification for the BPD/death outcome. The one with a missing BPD outcome is one of the Duke infants who had some data deleted that will hopefully be restored soon. However, there are 7 cases where resolution of the BPD queries could change the BPD classification for the physiologic definition, and 18 cases where query resolution could change the outcome for BPD by the supplemental O2 definition. Those are the queries that I have highlighted in the documents I just sent you.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 02, 2009 2:41 PM
To: Gantz, Marie
Subject: RE: SUPPORT missing data updates

How many final BPD outcomes are unresolved?

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 02, 2009 2:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil; Wally Carlo; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are the following:

1) A zipped file containing documents for each center with unresolved BPD queries. (Centers without a document have no outstanding queries.) Queries that have potential to change the BPD outcomes are highlighted in yellow. Other queries address missing forms (like the SUPP11) and other data inconsistencies that will not necessarily affect whether the infant is classified as having BPD or not.
2) A zipped file containing documents for each center with infants who are missing final ROP status. (Centers without a document have no outstanding ROP outcomes.) Note that these documents list all infants without a ROP final outcome, including those whom the centers have coded on the SUPP10 as having the acute ROP outcome missing at 55 weeks PMA and/or having not obtained final ROP status at the 18 month FU visit.
3) An Excel file with the usual missing data reminders for ROP, BPD and FU.

We are currently missing ROP on 104 infants: 4 have been withdrawn from the study, 1 with vessels in

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zone 1 at last exam, 47 with vessels in zone 2 at last exam, and 52 with vessels in zone 3 at last exam. However, the 104 also includes three infants who were found at follow-up to have died after discharge, two at about 7 months old, and one at about a year old. Thus, we are missing ROP outcomes for a total of 97 infants who have not died and who have not been withdrawn from the study.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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828-254-6255

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From: Finer, Neil
To: Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo
Cc: Abhik Das; Gantz, Marie
Subject: RE: SUPPORT AUTHORSHIP ORDER
Date: Thursday, October 01, 2009 7:53:40 PM

I like Rose as senior author
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, October 01, 2009 4:05 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo
Cc: Abhik Das; Gantz, Marie
Subject: RE: SUPPORT AUTHORSHIP ORDER

I would think Rose if she wants it or she may prefer to be third.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thursday, October 01, 2009 12:15 PM
To: 'Finer, Neil'; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo
Cc: Abhik Das; Gantz, Marie
Subject: RE: SUPPORT AUTHORSHIP ORDER

Who should be the "senior author" at the end of the list?

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, October 01, 2009 1:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo
Cc: Abhik Das; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT AUTHORSHIP ORDER

Hi Rose
I would suggest that for the CPAP-Surf paper the authors be Finer, Carlo followed by the order you suggest and that for the SpO2 paper the authors be Carlo, Finer and the order that you suggest. I would like Wade and Marie in the first 5 or 6 authors for each paper.
Well in fact the truth be told, I would prefer NO AUTHORS - but I won't go there!!

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Wade has played a key role in these trials. He and I essentially designed the offset oximeters, and he has also has been involved in looking at all the data and has been an effective author, reviewing all the results and each and every revision in detail.

The Boiler plate etc should be the same for both papers
Neil

On 10/1/09 5:59 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Neil and Wally
We need to develop the authorship order for SUPPORT. The subcommittee members are listed following you as the first author for each paper. Generally, the more involved folks on the subcommittee are ordered to the front of the list. After the subcommittee, the sites are listed (usually in recruitment order). The statistician(s) can be listed where ever you feel the effort dictates. Let me know if the two of you would like to discuss (we probably should have discussed this on Monday on our call), or we can do it by email. Stephanie can generate a title page with order and author affiliations.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Gantz, Marie
Subject: RE: Oxygen Saturation Manuscript
Date: Thursday, October 01, 2009 6:04:57 PM

Neil:

We should try to have a PAS abstract so only have a month or so.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, October 01, 2009 4:27 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Gantz, Marie
Subject: Re: Oxygen Saturation Manuscript

This looks good Wally
Now we wait for the ROP
I suspect we will be frustrated by the data.
Be well
Neil

On 10/1/09 1:53 PM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

Dear Rose, Neil, Abhik, and Marie:

Enclosed is the draft 5.0 of the O2 saturation paper. Thank you very much for getting your comments to me. I have heard from everyone in the group. I have made changes, essentially accepting every suggestion.

There are several remaining issues at this stage.

1. The saturation cut off of the monitors. I have stated that at less than 85% and higher than 95% displayed values return to actual values as this happens at 84% saturation and at 96% saturation. Thus, I thought it would be easier to state less than 85% and higher than 95% as these numbers are used clinically. We may want to instead use the symbols < or >. One person suggested to use less than or equal to 84% and greater than or equal to 96%. I am concerned that these numbers may be

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different to what most clinicians use in practice. I have reviewed the information we have from Massimo and the values less than 85% or higher than 95% may be the easier way for our readers to understand what we did.

2. There is a statement about safety outcomes monitored by DSMC. I am not sure what outcomes were monitored besides mortality, pneumothorax, and IVH. If there are others I can add them. Abhik: Were there other major outcomes monitored by the DSMB?
3. Figure 2 still needs the final numbers. I have not changed the figure. I have also not changed the tables or the numbers in the text, pending the final updated data.

Obviously once we get more data, some of the wording (particularly the results and discussion) will change. However, I think we should try to have as near a final manuscript as soon as possible, pending final data.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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From: Wally Carlo, M.D.
Subject: RE: BPD edits and other issues
Date: Thursday, October 01, 2009 4:51:38 PM

We need these to make the papers more final.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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619 South 20th Street
525 New Hillman Building
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 01, 2009 2:06 PM
To: 'Gantz, Marie'; Finer, Neil; Wally Carlo, M.D.
Cc: Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: BPD edits and other issues

I think I should send the BPD queries

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, October 01, 2009 12:17 PM
To: Finer, Neil; Wally Carlo
Cc: Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: BPD edits and other issues

Thanks for the manuscript, Neil.

I have checked all the BPD queries we sent in July, and there are still 74 infants with issues that need to be cleared up. The good news is that most centers have 5 or fewer. I count a total of 8 queries that could impact the infant's classification of BPD by the physiologic definition and 17 that could impact the outcome of BPD by supplemental O2 use. In addition, there are 27 cases where we are missing SUPP11 forms and BPD is currently being set based on NG07 data. This is important because I have been checking the NG07 against the SUPP11 for consistency and in these 27 cases I have not been able to do those checks. Thus, once the SUPP11s are entered we could find that there are additional inconsistencies that need to be cleared up. Note that some of the 74 queries mentioned above are actually new queries that arose because additional SUPP11s were entered as a result of the previous round of queries and they were found to conflict with the NG07 data.

Do you want RTI to send out the new BPD queries/reminders or do you want

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Rose to send them again? I can highlight the queries that I know might change the BPD outcome so that the centers can address them with high priority.

As you all know, Michele Walsh and I were on a call this week regarding code being developed at RTI for the consensus definition of BPD. A couple of issues arose during the call that also impact the BPD outcomes for SUPPORT. One was the issue of how babies on RA by vent or CPAP should be classified (for the traditional BPD outcome) which Rose also brought up this week (there are 18 such cases in the SUPPORT data). Michele suggested that if we had an adjudication committee these babies could be part of the group that the committee would review. Another group of concern was those who qualified for the room air challenge but were not challenged due to 'instability' (N=2) or for 'other' reasons (N=25). Some of those 'other' reasons were things like 'personnel not available' but some were more informative. Long ago I had sent Neil a spreadsheet listing those 'other' reasons, but if there is an adjudication committee perhaps those infants should be included in the group that are reviewed. Another group that the committee might look at is those who were on vent for surgery - I have identified 3 such cases from the PHY01 reasons challenge not done and F5s on the NG07.

Finally, the other thing I need to look at are the cross-form queries to address inconsistencies such as IVH reported on one form but not another. We have received responses from 11 of the centers for these queries that were sent out in early September. I will look at these responses and outstanding queries and let you know what the status is.

Wade, I will try to re-run your analyses next week.

Marie

Marie Gantz, Ph.D.
Research Statistician
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mgantz@rti.org
828-254-6255
-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 29, 2009 1:44 PM
To: Wally Carlo; Gantz, Marie
Cc: Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Manuscript CPAP vs Surf

Hi Marie
Please find attached the revised manuscript which has all of Wally's changes
Please use this one when you correct the numbers etc
Thanks
If we are going to be delayed for the ROP outcomes, I think that we should
consider getting this paper to NEJM first - they may have an issue receiving
both of them and then we can relax as we await the ROP data
Your thoughts

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Also Marie - when will Wades data be ready so that we can submit that manuscript
Thanks
Neil

On 9/28/09 4:07 PM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

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> Enclosed are my tracked suggestions.
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> In addition a few comments:
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> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Monday, September 28, 2009 3:18 PM
> To: Gantz, Marie
> Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
> Subject: SUPPORT Manuscript CPAP vs Surf
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> Hello Marie
> Here is the current manuscript
> Please check for accuracy and numbers
> Lets remove the adjusted from the p values.
> Please make any other changes you think will benefit
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> Many thanks
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From: Wally Carlo, M.D.
Subject: RE: BPD edits and other issues
Date: Thursday, October 01, 2009 4:51:03 PM

I agree. With a deadline!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT!
Date: Thursday, October 01, 2009 2:57:17 PM

OK, I will run those now (and do it weekly for the next three weeks). Thanks!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 01, 2009 2:53 PM
To: Gantz, Marie
Subject: RE: SUPPORT!

Marie
Weekly reports would be terrific.

Can you generate a list of ALL missing ROP final outcomes for one more chance at the sites (in case they can find a late exam). Please indicate if the site has reported these infants as "lost" on the ROP outcome.

I think we need to generate the report weekly for the next three weeks in hopes of getting the stragglers. (If not too much to ask)

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, October 01, 2009 2:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT!

Rose,

As of this weeks' data we are missing final ROP status on 96 infants who have not died or been withdrawn from the study, and 38 of them have been coded by the centers on the SUPP10 as having the acute outcome lost to FU at 55 weeks and/or having not obtained the final ROP status at the 18 month FU visit. Thus, ROP missing data reminders are not generated for those 38 infants when I run the report every 2 weeks. For the request below, I have looked at Case's data and they only have the one lost to FU infant without a ROP outcome (which is terrific, and I will send them an email to confirm that's the only missing case). But, for the other centers, do you want me to generate a list of *all* infants who are missing the ROP outcome, or just continue to send reminders for those who have *not* been coded as lost?

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Also, you mentioned on Monday's phone call that you would like me to generate the missing outcomes report this week. That is fine, but I wanted to double-check that was what you wanted since the reports were generated last week (and generally we do them every 2 weeks).

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 29, 2009 1:24 PM
To: Gantz, Marie
Subject: Fw: SUPPORT!

Please let them know

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Bonnie Siner <bss5@case.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Walsh, Michele' <Michele.Walsh@UHhospitals.org>
Sent: Tue Sep 29 12:46:11 2009
Subject: RE: SUPPORT!

I know all our ROP data is complete, with 1 that I recall as LTFU.
Can we get our center's list of 'infants without an ROP outcome' ?

Bonnie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 28, 2009 3:06 PM
To: 'Finer, Neil'; 'Sood, Beena'; 'Susie Buchter'; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT!!!

There are 109 infants without an ROP outcome in the SUPPORT trial (n=1317). We need to finalize and lock the ROP data so that the analysis can proceed. The final date for Data Entry

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for SUPPORT ROP is OCTOBER 20. Please insure that you have the outcomes for your infants entered by October 20!!!

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
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301-496-5575
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From: Das, Abhik
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NeoProM Data query
Date: Thursday, October 01, 2009 1:06:52 PM

Was this part of the original data request? I don't remember whether we discussed this before; perhaps we need direction from the steering committee. However, since multiple births are design variables for our study, I don't see how they can do any analysis without that information.

Thanks

Abhik

From: Gantz, Marie
Sent: Thursday, October 01, 2009 12:30 PM
To: Das, Abhik; 'Kylie Hunter'
Subject: RE: NeoProM Data query

Kylie,

We do have information on birth order and sibling match in our data; however, there is a question of whether we can share that information due to privacy issues. For example, if there is a set of quadruplets that might be a rare enough occurrence that sharing the information would make the infants identifiable. There is the additional complication that cases of multiple births in SUPPORT were randomized as a group (the pregnancy, not the infant, was the unit of randomization). Thus, family is one of our design variables that we control for in our analyses. Abhik is currently out of the office, but when he returns we will try to resolve this issue and figure out what information we can and cannot share.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Das, Abhik
Sent: Wednesday, September 30, 2009 10:15 AM
To: Kylie Hunter
Cc: Gantz, Marie
Subject: RE: NeoProM Data query

I have forwarded your query to Dr. Gantz.

Thanks

Abhik

From: Kylie Hunter [mailto:kylie.hunter@ctc.usyd.edu.au]
Sent: Wednesday, September 30, 2009 3:29 AM

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To: Das, Abhik
Subject: NeoProM Data query

Dear Abhik,

I have taken over from Charlene Thornton at the NHMRC CTC in assisting Lisa Askie with NeoProM. I have been reviewing a spreadsheet mapping data items (attached), and there is a note for me to double check some details of the SUPPORT trial with Marie Gantz. However, we don't seem to have Marie's email address on record. If you could please provide us with this address and forward her this email that would be great thank you.

The query relates to two Enrolment characteristics:

1) Birth order; and
2) Sibling match.

The spreadsheet indicates that this data is not available in the SUPPORT trial, however, Lisa has asked me to clarify this with Marie.

If you could please review the attached spreadsheet and clarify this, that would be very helpful.

Thank you and kind regards,

Kylie Hunter (on behalf of Lisa Askie)

Systematic Reviews Project Officer
NHMRC Clinical Trials Centre, University of Sydney
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CAMPERDOWN NSW 2050
+61 2 9562 5031
kylie.hunter@ctc.usyd.edu.au

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From: Finer, Neil
To: Gantz, Marie; Wally Carlo
Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: Re: BPD edits and other issues
Date: Thursday, October 01, 2009 12:40:46 PM

Hi Marie
We will use the BPD definition - non-physiologic- as the need for oxygen at 36 weeks. We can later separately report if we like in a subsequent paper the number of infants on vents/CPAP and room air but we will not use this for the BPD assessment. We have already discussed that some of these infants were on vents/CPAP because of recent surgery etc and this will only lead to confusion. We need to be mindful of the ability to compare our results with other studies like COIN and the we should use the commonly accepted definitions for now.
We do need clarity on the true numbers for oxygen at 36 weeks and so for me, these are the primary concerns.
In addition we should clean up as well as possible the physiologic definition and allocations as well as we can. You and I had looked at the Physiologic Infants and we had agreed on their allocation. However, I am OK if others want to have another go at this
To get the best response I would suggest that you and Rose send these out together.
Thanks
Neil

On 10/1/09 9:17 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

> Thanks for the manuscript, Neil.
>
> I have checked all the BPD queries we sent in July, and there are still
> 74 infants with issues that need to be cleared up. The good news is that
> most centers have 5 or fewer. I count a total of 8 queries that could
> impact the infant's classification of BPD by the physiologic definition
> and 17 that could impact the outcome of BPD by supplemental O2 use. In
> addition, there are 27 cases where we are missing SUPP11 forms and BPD
> is currently being set based on NG07 data. This is important because I
> have been checking the NG07 against the SUPP11 for consistency and in
> these 27 cases I have not been able to do those checks. Thus, once the
> SUPP11s are entered we could find that there are additional
> inconsistencies that need to be cleared up. Note that some of the 74
> queries mentioned above are actually new queries that arose because
> additional SUPP11s were entered as a result of the previous round of
> queries and they were found to conflict with the NG07 data.
>
> Do you want RTI to send out the new BPD queries/reminders or do you want
> Rose to send them again? I can highlight the queries that I know might
> change the BPD outcome so that the centers can address them with high
> priority.
>
> As you all know, Michele Walsh and I were on a call this week regarding
> code being developed at RTI for the consensus definition of BPD. A
> couple of issues arose during the call that also impact the BPD outcomes
> for SUPPORT. One was the issue of how babies on RA by vent or CPAP

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> should be classified (for the traditional BPD outcome) which Rose also
> brought up this week (there are 18 such cases in the SUPPORT data).
> Michele suggested that if we had an adjudication committee these babies
> could be part of the group that the committee would review. Another
> group of concern was those who qualified for the room air challenge but
> were not challenged due to 'instability' (N=2) or for 'other' reasons
> (N=25). Some of those 'other' reasons were things like 'personnel not
> available' but some were more informative. Long ago I had sent Neil a
> spreadsheet listing those 'other' reasons, but if there is an
> adjudication committee perhaps those infants should be included in the
> group that are reviewed. Another group that the committee might look at
> is those who were on vent for surgery - I have identified 3 such cases
> from the PHY01 reasons challenge not done and F5s on the NG07.
>
> Finally, the other thing I need to look at are the cross-form queries to
> address inconsistencies such as IVH reported on one form but not
> another. We have received responses from 11 of the centers for these
> queries that were sent out in early September. I will look at these
> responses and outstanding queries and let you know what the status is.
>
> Wade, I will try to re-run your analyses next week.
>
> Marie
>
>
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, September 29, 2009 1:44 PM
> To: Wally Carlo; Gantz, Marie
> Cc: Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
> Subject: Re: SUPPORT Manuscript CPAP vs Surf
>
> Hi Marie
> Please find attached the revised manuscript which has all of Wally's
> changes
> Please use this one when you correct the numbers etc
> Thanks
> If we are going to be delayed for the ROP outcomes, I think that we
> should
> consider getting this paper to NEJM first - they may have an issue
> receiving
> both of them and then we can relax as we await the ROP data
> Your thoughts
> Also Marie - when will Wades data be ready so that we can submit that
> manuscript
> Thanks
> Neil
>
>
> On 9/28/09 4:07 PM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:
>

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>> Hi Neil:
>>
>> Enclosed are my tracked suggestions.
>>
>> In addition a few comments:
>>
>> 1. I think the abstract is a bit long.
>> 2. The use of decimals in the p values is usually restricted to 3
> (e.g.
>> P < 0.001 not P < 0.0001).
>> 3. You may want to change from "need of O2" to "on O2".
>>
>> Way to go!
>> wally
>>
>> Wally Carlo, M.D.
>> Edwin M. Dixon Professor of Pediatrics
>> University of Alabama at Birmingham
>> Director, Division of Neonatology
>> Director, Newborn Nurseries
>> 619 South 20th Street
>> 525 New Hillman Building
>> Birmingham, AL 35233-7335
>> Phone: 205 934 4680
>> FAX: 205 934 3100
>> Cell: 205 266 (b)
>>
>> -----Original Message-----
>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>> Sent: Monday, September 28, 2009 3:18 PM
>> To: Gantz, Marie
>> Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Wally
>> Carlo, M.D.
>> Subject: SUPPORT Manuscript CPAP vs Surf
>>
>> Hello Marie
>> Here is the current manuscript
>> Please check for accuracy and numbers
>> Lets remove the adjusted from the p values.
>> Please make any other changes you think will benefit
>> I will circulate once I have seen your corrections
>> Many thanks
>> Neil
>

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From: Phelps, Dale
To: Finer, Neil
Cc: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade; Gantz, Marie
Subject: RE: SUPPORT Subcommittee Meeting
Date: Thursday, October 01, 2009 3:08:00 AM

Hi Neil,

This is not a simple answer: but if you insist, 'not very comfortable.'

Question: "If an infant has a single Zone 3 exam and did not reach previous threshold or Stage 3 and did not have surgery, how comfortable would you be to say that this infant did not have significant ROP?"
Premise: one examination in zone III, not previously threshold (you imply there were other previous exams)
1a. If there never was ROP before, then adjudication may give this infant a secondary outcome of 'never threshold' (but not a primary outcome). The findings in zone III would influence this. For example, if there were stage 3 in zone III, I doubt any adjudication could be 'favorable'.

1b. If there were significant previous ROP (even stage 2) and it is now regressing and into zone III for the first time, but infant was never seen again, there is no primary outcome. Adjudication may given this infant a secondary outcome of "not serious ROP", or may give an outcome of "We'll never know."

We found that infants with some ROP or even no ROP that had zone III diagnosed, subsequently had zone II ROP diagnosed on the next examination 12% of the time. That is why we require zone III for two SEQUENTIAL examinations before we consider the infant to be 'home free'.

Dale

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 29, 2009 1:46 PM
To: Phelps, Dale
Cc: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Rich, Wade; Gantz, Marie
Subject: Re: SUPPORT Subcommittee Meeting

Hi Dale
We are looking at the data and making a final push to get the most recent information One question - If an infant has a single Zone 3 exam and did not reach previous threshold or Stage 3 and did not have surgery, how comfortable would you ne to say that this infant did not have significant ROP?
Many thanks for your willingness to be involved I can only say that for any future study, these eye outcomes will need additional thought as it relates to obtaining a final exam available to the site/study center.
Be well
Neil

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On 9/29/09 11:54 AM, "Dale Phelps" <Dale_Phelps@URMC.Rochester.edu> wrote:

Hi Neil,

To date, we have confirmed one ophthalmologist to adjudicate the ROP uncertain outcomes, and he has identified a second, but we have not yet confirmed her.

I am working on a third (and in a pinch, could do that myself.)

Is there anything else I can do to help you prepare for your Subcomittee meeting in regards to the ROP ?

Dale

Dale Phelps
Professor of Pediatrics
30250 S.Highway 1
Gualala, CA 95445
Ph. (707) 897-9063

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; mgantz@rti.org; Wally Carlo
Cc: Abhik Das; Zaterka-Baxter, Kristin
Subject: RE: Final outcome assignments for SUPPORT
Date: Wednesday, September 30, 2009 1:13:19 PM

Yes! The definition of BPD is oxygen and/or resp support at 36 weeks.
Thus, it is my belief that they are on respiratory support
And thus should be counted as BPD. This was the subject of
Our working group conference call yesterday.
From our work with the consensus definition and Physiologic Def,
There is some risk that babes who are in RA and cpap/vent with strictly
airway issues could Be misclassified as BPD, but this was only 3 out of
about 3400 babes in the Bench trial, and thus seems an acceptable
tradeoff to me to avoid missing those with true BPD. WE refined the
algorithm for
Diagnosis yesterday in our conference call.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 30, 2009 8:46 AM
To: 'Finer, Neil'; Walsh, Michele; mgantz@rti.org; Wally Carlo
Cc: Abhik Das; 'Zaterka-Baxter, Kristin'
Subject: RE: Final outcome assignments for SUPPORT

I can get this set up - do we need an ophthalmologist(s) and if so, how many?

Also - one more item that has come up -

Infants who are on CPAP or some type of vent support at 36 weeks (When NG07 gets filled out for BPD)but are on room air or 21% oxygen? Should they be in the BPD group (not eligible for physio challenge because they are "too sick", but if one uses "oxygen at 36 weeks" as BPD definition, they are classified as "no BPD.")

Rose

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 29, 2009 4:55 PM
To: Walsh, Michele; mgans@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
Cc: Abhik Das
Subject: Re: Final outcome assignments for SUPPORT

I am OK with doing this and would be willing to serve
Neil

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On 9/29/09 12:52 PM, "Walsh, Michele" <Michele.Walsh@UHhospitals.org> wrote:

Hi All: Marie and I were on a conference call today regarding the algorithm for the Consensus definition and physiologic definitions of BPD.
As we talked, it became clear that there would be some cases (?? <3%) that would be special cases that are unlikely to be clearly Classified by a computer algorithm. I would propose that the SUPPORT Subcommittee form an adjudication committee to deal with those unusual cases
In the same way that Hypothermia had an adjudication committee to assign Neurodevelopmental outcomes. To provide the most integrity to the trial,
The adjudication committee would need to have the following prespecified Characteristics:

1. an odd number of members (so that ties can not occur)
2. Independent review of cases and assignment of outcomes by each

Member using an agreed upon hierarchy of data. Clear definition of When available data are insufficient to assign outcome and thus outcome Is assigned as "Lost".

3. Written submission of the outcomes to RTI by each member.

1. Assignment of the outcome by majority of the committee.
2. in cases where no clear majority outcome assignment, conference

call and discussion until outcome clearly assigned.
If the SUPPORT subcommittee decides to go forward with such a process, I would be pleased to be part of the BPD adjudication committee.
Best,
Michele Walsh
Medical Director NICU
Rainbow Babies & Childrens Hospital
Case Medical Center
Professor, Deparment of Pediatrics
Case Western Reserve University
phone: 216-844-3759
FAX: 216-844-3380
michele.walsh@cwru.edu <mailto:michele.walsh@cwru.edu>
michele.walsh@UHhospitals.org <mailto:michele.walsh@UHhospitals.org>
(emails are interchangeable)

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From: Walsh, Michele
To: Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Cc: Abhik Das; Zaterka-Baxter, Kristin
Subject: RE: Final outcome assignments for SUPPORT
Date: Wednesday, September 30, 2009 12:46:25 PM

I agree that it may also be helpful to
Have an ROP adjudication committee. For example,
We have one pt who had exams up to 49 weeks
Without any ROP. Without a committee, the computer
Would see this pt as missing an outcome. There is real information
Available that can yield an outcome assessment... and thus
More information for the trial. So long as they are tracked and reported
Clearly, my thought is more information is better.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 30, 2009 11:22 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; mgantz@rti.org
Cc: Abhik Das; Zaterka-Baxter, Kristin
Subject: RE: Final outcome assignments for SUPPORT

I see it more as making recommendation on how to adjudicate the outcome.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 30, 2009 10:12 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; mgantz@rti.org
Cc: Abhik Das; Zaterka-Baxter, Kristin
Subject: Re: Final outcome assignments for SUPPORT

My opinion is that they will not offer much help. Missing data is
missing -
we are going to be speculating and in some circumstances possibly second
guessing the actual examiner.
Neil

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On 9/30/09 6:30 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

> I want opinions on the ROP committee-
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Wednesday, September 30, 2009 9:29 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Walsh, Michele;
> mgantz@rti.org
> Cc: Abhik Das; Zaterka-Baxter, Kristin
> Subject: RE: Final outcome assignments for SUPPORT
>
> Rose:
>
> This one is for the BPD adjudication. I think we should also go ahead
> and set up the adjudication committee for ROP.
> Wally
>
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Wednesday, September 30, 2009 7:46 AM
> To: 'Finer, Neil'; Walsh, Michele; mgantz@rti.org; Wally Carlo, M.D.
> Cc: Abhik Das; 'Zaterka-Baxter, Kristin'
> Subject: RE: Final outcome assignments for SUPPORT
>
> I can get this set up - do we need an ophthalmologist(s) and if so,
how
> many?
>
> Also - one more item that has come up -
>
> Infants who are on CPAP or some type of vent support at 36 weeks (When
> NG07 gets filled out for BPD)but are on room air or 21% oxygen?
Should
> they be in the BPD group (not eligible for physio challenge because
they
> are "too sick", but if one uses "oxygen at 36 weeks" as BPD
definition,
> they are classified as "no BPD.")
>
> Rose

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>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, September 29, 2009 4:55 PM
> To: Walsh, Michele; mgans@rti.org; Higgins, Rosemary (NIH/NICHD) [E];
> Wally Carlo
> Cc: Abhik Das
> Subject: Re: Final outcome assignments for SUPPORT
>
> I am OK with doing this and would be willing to serve
> Neil
>
>
> On 9/29/09 12:52 PM, "Walsh, Michele" <Michele.Walsh@UHhospitals.org>
> wrote:
>
> Hi All: Marie and I were on a conference call today regarding the
> algorithm for the Consensus definition and physiologic definitions of
> BPD.
> As we talked, it became clear that there would be some cases
> (?? <3%) that would be special cases that are unlikely to be clearly
> Classified by a computer algorithm. I would propose that the SUPPORT
> Subcommittee form an adjudication committee to deal with those unusual
> cases
> In the same way that Hypothermia had an adjudication committee to
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> trial,
> The adjudication committee would need to have the following
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> Characteristics:
>
> 1. an odd number of members (so that ties can not occur)
> 2. Independent review of cases and assignment of outcomes by each
>
> Member using an agreed upon hierarchy of data. Clear definition of
> When available data are insufficient to assign outcome and thus
outcome
> Is assigned as "Lost".
> 3. Written submission of the outcomes to RTI by each member.
>
> 1. Assignment of the outcome by majority of the committee.
> 2. in cases where no clear majority outcome assignment, conference
>
> call and discussion until outcome clearly assigned.
> If the SUPPORT subcommittee decides to go forward with such a process,
> I would be pleased to be part of the BPD adjudication committee.
> Best,
> Michele Walsh
> Medical Director NICU
> Rainbow Babies & Childrens Hospital
> Case Medical Center
> Professor, Deparment of Pediatrics
> Case Western Reserve University
> phone: 216-844-3759
> FAX: 216-844-3380
> michele.walsh@cwru.edu <mailto:michele.walsh@cwru.edu>

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> michele.walsh@UHhospitals.org <mailto:michele.walsh@UHhospitals.org>
> (emails are interchangeable)
>
>
>
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From: Finer, Neil
To: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; mgantz@rti.org
Cc: Abhik Das; Zaterka-Baxter, Kristin
Subject: Re: Final outcome assignments for SUPPORT
Date: Wednesday, September 30, 2009 10:55:52 AM

That's fine with me
Neil

On 9/30/09 6:34 AM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

> Rose:
>
> I think maybe you, Dale, and an ophthalmologist should constitute the
> ROP adjudication committee.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b)
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Wednesday, September 30, 2009 8:31 AM
> To: Wally Carlo, M.D.; Finer, Neil; Walsh, Michele; mgantz@rti.org
> Cc: Abhik Das; Zaterka-Baxter, Kristin
> Subject: RE: Final outcome assignments for SUPPORT
>
> I want opinions on the ROP committee-
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Wednesday, September 30, 2009 9:29 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Walsh, Michele;
> mgantz@rti.org
> Cc: Abhik Das; Zaterka-Baxter, Kristin
> Subject: RE: Final outcome assignments for SUPPORT
>
> Rose:
>
> This one is for the BPD adjudication. I think we should also go ahead
> and set up the adjudication committee for ROP.
> Wally
>
>

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> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Wednesday, September 30, 2009 7:46 AM
> To: 'Finer, Neil'; Walsh, Michele; mgantz@rti.org; Wally Carlo, M.D.
> Cc: Abhik Das; 'Zaterka-Baxter, Kristin'
> Subject: RE: Final outcome assignments for SUPPORT
>
> I can get this set up - do we need an ophthalmologist(s) and if so, how
> many?
>
> Also - one more item that has come up -
>
> Infants who are on CPAP or some type of vent support at 36 weeks (When
> NG07 gets filled out for BPD)but are on room air or 21% oxygen? Should
> they be in the BPD group (not eligible for physio challenge because they
> are "too sick", but if one uses "oxygen at 36 weeks" as BPD definition,
> they are classified as "no BPD.")
>
> Rose
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, September 29, 2009 4:55 PM
> To: Walsh, Michele; mgans@rti.org; Higgins, Rosemary (NIH/NICHD) [E];
> Wally Carlo
> Cc: Abhik Das
> Subject: Re: Final outcome assignments for SUPPORT
>
> I am OK with doing this and would be willing to serve
> Neil
>
>
> On 9/29/09 12:52 PM, "Walsh, Michele" <Michele.Walsh@UHhospitals.org>
> wrote:
>
> Hi All: Marie and I were on a conference call today regarding the
> algorithm for the Consensus definition and physiologic definitions of
> BPD.
> As we talked, it became clear that there would be some cases
> (?? <3%) that would be special cases that are unlikely to be clearly
> Classified by a computer algorithm. I would propose that the SUPPORT
> Subcommittee form an adjudication committee to deal with those unusual
> cases
> In the same way that Hypothermia had an adjudication committee to assign
> Neurodevelopmental outcomes. To provide the most integrity to the

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> trial,
> The adjudication committee would need to have the following prespecified
> Characteristics:
>
> 1. an odd number of members (so that ties can not occur)
> 2. Independent review of cases and assignment of outcomes by each
>
> Member using an agreed upon hierarchy of data. Clear definition of
> When available data are insufficient to assign outcome and thus outcome
> Is assigned as "Lost".
> 3. Written submission of the outcomes to RTI by each member.
>
> 1. Assignment of the outcome by majority of the committee.
> 2. in cases where no clear majority outcome assignment, conference
>
> call and discussion until outcome clearly assigned.
> If the SUPPORT subcommittee decides to go forward with such a process,
> I would be pleased to be part of the BPD adjudication committee.
> Best,
> Michele Walsh
> Medical Director NICU
> Rainbow Babies & Childrens Hospital
> Case Medical Center
> Professor, Deparment of Pediatrics
> Case Western Reserve University
> phone: 216-844-3759
> FAX: 216-844-3380
> michele.walsh@cwru.edu <mailto:michele.walsh@cwru.edu>
> michele.walsh@UHhospitals.org <mailto:michele.walsh@UHhospitals.org>
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From: Wally Carlo, M.D.
To: Finer, Neil; Walsh, Michele; mgans@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Abhik Das
Subject: RE: Final outcome assignments for SUPPORT
Date: Tuesday, September 29, 2009 5:30:55 PM

I am also willing to serve on it. We can agree on criteria and then individually adjudicate babies as Michele says.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 29, 2009 3:55 PM
To: Walsh, Michele; mgans@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Abhik Das
Subject: Re: Final outcome assignments for SUPPORT

I am OK with doing this and would be willing to serve
Neil

On 9/29/09 12:52 PM, "Walsh, Michele" <Michele.Walsh@UHhospitals.org> wrote:

Hi All: Marie and I were on a conference call today regarding the algorithm for the Consensus definition and physiologic definitions of BPD.
As we talked, it became clear that there would be some cases (?? <3%) that would be special cases that are unlikely to be clearly Classified by a computer algorithm. I would propose that the SUPPORT Subcommittee form an adjudication committee to deal with those unusual cases
In the same way that Hypothermia had an adjudication committee to assign Neurodevelopmental outcomes. To provide the most integrity to the trial,
The adjudication committee would need to have the following prespecified Characteristics:

1. an odd number of members (so that ties can not occur)
2. Independent review of cases and assignment of outcomes by each

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Member using an agreed upon hierarchy of data. Clear definition of
When available data are insufficient to assign outcome and thus outcome
Is assigned as "Lost".

3. Written submission of the outcomes to RTI by each member.

1. Assignment of the outcome by majority of the committee.
2. in cases where no clear majority outcome assignment, conference

call and discussion until outcome clearly assigned.
If the SUPPORT subcommittee decides to go forward with such a process,
I would be pleased to be part of the BPD adjudication committee.
Best,

Michele Walsh
Medical Director NICU
Rainbow Babies & Childrens Hospital
Case Medical Center
Professor, Deparment of Pediatrics
Case Western Reserve University
phone: 216-844-3759
FAX: 216-844-3380
michele.walsh@cwru.edu <mailto:michele.walsh@cwru.edu>
michele.walsh@UHhospitals.org <mailto:michele.walsh@UHhospitals.org>
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From: Finer, Neil
To: Wally Carlo; Gantz, Marie
Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Manuscript CPAP vs Surf
Date: Tuesday, September 29, 2009 1:45:19 PM
Attachments: SUPPORT CPAP vs Surf Sept 29 09 .docx

Hi Marie
Please find attached the revised manuscript which has all of Wally's changes
Please use this one when you correct the numbers etc
Thanks
If we are going to be delayed for the ROP outcomes, I think that we should consider getting this paper to NEJM first - they may have an issue receiving both of them and then we can relax as we await the ROP data
Your thoughts
Also Marie - when will Wades data be ready so that we can submit that manuscript
Thanks
Neil

On 9/28/09 4:07 PM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

> Hi Neil:
>
> Enclosed are my tracked suggestions.
>
> In addition a few comments:
>
> 1. I think the abstract is a bit long.
> 2. The use of decimals in the p values is usually restricted to 3 (e.g.
> P < 0.001 not P < 0.0001).
> 3. You may want to change from "need of O2" to "on O2".
>
> Way to go!
> wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 619 South 20th Street
> 525 New Hillman Building
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 266 (b) (6)
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Monday, September 28, 2009 3:18 PM
> To: Gantz, Marie
> Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Wally
> Carlo, M.D.

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> Subject: SUPPORT Manuscript CPAP vs Surf
>
> Hello Marie
> Here is the current manuscript
> Please check for accuracy and numbers
> Lets remove the adjusted from the p values.
> Please make any other changes you think will benefit
> I will circulate once I have seen your corrections
> Many thanks
> Neil

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Address correspondence to

Neil Finer, MD

402 Dickenson St, 8774

San Diego, Ca, 92103-8774

Email – nfiner@ucsd.edu

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks and 26 to 27 6/7th weeks. Infants were randomized to CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1317 infants from January 1 2004 to March 1 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.001$). The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, $p=0.03$). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.015$). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, ($p<0.001$). There were no differences between the groups for airleaks including pneumothoraces.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months.

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Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation

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or CPAP at 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses~~4~~6, and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of 24 to 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision had been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses was a logistic regression analysis of the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks and on the percent infants who survive without neurodevelopmental sequelae at 2 years. Adjustment was performed as pre-specified for gestational age, center and familial clustering. A two-sided P value of less than 0.05 was considered to statistically significant. An independent data safety monitoring committee reviewed the interim results, including those concerning adverse outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

The study was approved by Human Subjects Committees at all participating sites and RTI, the data center, and parental consent was required before delivery.

Results:

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There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 . The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 groups. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm for the 24 to 25 week strata. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, $p=0.27$. Using the Physiologic Definition for BPD there was no decrease in the occurrence of BPD in the CPAP group (40% vs 41%, $p=0.96$), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, $p=0.32$).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.01$). There were no differences between the groups in air leaks in the first 14 days, airleaks during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, $p<.001$).

Strata Results: 24 – 25 weeks Gestation

There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, $p=0.03$. There was a significantly higher exposure to

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postnatal steroids for BPD, 21% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p<0.01, lesser days of mechanical ventilation, 10.7 vs 14.2, p<0.01, and less postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first multicenter trial to compare early CPAP with early surfactant given within an hour of life in ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[14][14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our method of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.**[8] We believed that testing this complete approach would provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a significant reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. We also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

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Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Sat paper
Date: Tuesday, September 29, 2009 7:53:46 AM

Rose:

Great! I will work on the next draft.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 29, 2009 5:48 AM
To: Wally Carlo, M.D.
Subject: Sat paper

Wally
I looked this over and have to admit it is hard writing not knowing what the data will shiow.
Comments -
Page 4 - second paragraph - pulse ox's have been in NICUs more than 20 years (remove "recent").
Page 6 - patients - change "decision to forgo "support" to "resuscitation"
Page 6 - ok to say we used Masimo oximeters (and location of purchase).
Sat alarm ranges (less than or equal to 84 and greater than or equal to 96, right?)
ROP assessments - don't we need a minimum number of clock hours of disease?
Avastin was,kt a predefined outcome, bt we did collect the data.
Page 8 power analysis - do Marie's comments mirror the protocol?
For results, we can say the enrollemnt was temporarily paused after evaluation by DSMC and decision of NICHD director (the language on clintrials.gov is good). Again for restarting the trial (nichd director).
How is pvl data determined (this is impt as we will separately want to report the neuroimaging and would like consistency).
Thanks - more to come once we have data!!
Rose
Rosemary D. Higgins, MD
Program Scientist

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From: Wally Carlo, M.D.
To: Finer, Neil; Gantz, Marie
Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Manuscript CPAP vs Surf
Date: Monday, September 28, 2009 7:07:27 PM
Attachments: SUPPORT CPAP vs Surf Sept 28 09 .docx

Hi Neil:

Enclosed are my tracked suggestions.

In addition a few comments:

1. I think the abstract is a bit long.
2. The use of decimals in the p values is usually restricted to 3 (e.g. $P < 0.001$ not $P < 0.0001$).
3. You may want to change from "need of O2" to "on O2".

Way to go!
wally

Wally Carlo, M.D.
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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, September 28, 2009 3:18 PM
To: Gantz, Marie
Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: SUPPORT Manuscript CPAP vs Surf

Hello Marie
Here is the current manuscript
Please check for accuracy and numbers
Lets remove the adjusted from the p values.
Please make any other changes you think will benefit
I will circulate once I have seen your corrections
Many thanks
Neil

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks, and 26 to 27 6/7th weeks. Infants randomized to CPAP ~~were treated with CPAP~~ initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a -low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1317 infants from February 2005 to February 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all p<0.001). The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, (p < 0.05, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, p=0.03). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, (p<0.001). There were no differences between the groups for airleaks including pneenumothoraces.

~~The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, (p < 0.05, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, p=0.03).~~

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Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or ~~survival with~~ BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.~~,~~

Neil:

I think the abstract is a bit long but it can be shortened later if needed.

Introduction:

At the present time, there is no agreement as to the optimal approach to respiratory support for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC), and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9 hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[6,7] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8,9,10]

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The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age~~,~~ and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP at~~received~~ 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group~~, most occurring within the first 2 days~~ (9.1% vs 3.0%, p=.001), most occurring within the first 2 days, consistent with the findings of an earlier meta analyses~~46~~ , and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a ~~prospective,~~ randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen -using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this trial~~study~~ was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a

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permissive ventilatory strategy in infants of 24 to ~~less than~~ 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were ~~-~~24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision has ~~-~~ been made to provide full resuscitation, without known malformations, and for whom parental consent had been obtained. The infants were randomized to ~~-~~2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths~~-~~27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the ~~Neopuff~~ T-piece resuscitator or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery~~-~~. While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, ~~-~~an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50%~~-~~, a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for i~~I~~ntubation ~~for the CPAP infants~~. After 3 intubations CPAP infants were treated using NICU standard of care.

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Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses was a logistic regression analysis of the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks and on the percent infants who survive without neurodevelopmental sequelae at 2 years. Adjustment was performed as pre-specified for gestational age, center and familial clustering. A two-sided P value of less than 0.05 was considered to statistically significant. An independent data safety monitoring committee reviewed the interim results, including those concerning adverse

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outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

The study was approved by Human Subjects Committees at all participating sites and RTI, the data center, and parental consent was required before delivery.

Results:

There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009 (you use different dates than the abstract). The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus ~~Early~~ Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, Apgar scores or race between the 2 groups~~, although there were more boys in the CPAP arm, p=.056~~. The Surfactant group received significantly more epinephrine in the delivery room and had a trend for higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm the 24 to 25 week strata even after adjustment which included gender. There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, p=0.27. Using the Physiologic Definition for BPD there was no~~a non significant~~ decrease in the occurrence of BPD in the CPAP group (-40% vs 41%, p=0.96), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=0.32).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.0149). ~~We prospectively~~

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~~recorded~~ T~~air leaks in the first 14 days and t~~here were no differences between the groups~~, and no differences~~ in~~for~~ air leaks in the first 14 days, airleaks during the hospital stay, medical or surgical NEC, PDA requiring surgery, or severe IVH~~ or airleaks during the hospital stay~~. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs 13%, $p=0.0004$).

~~Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm the 24 to 25 week strata even after adjustment which included gender.~~

Strata Results: 24 – 25 weeks Gestation

There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, $p=0.03$. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, $p=0.02$ for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, $p<0.01$, lesser days of mechanical ventilation, 10.7 vs 14.2, $p<0.01$, and less postnatal steroids for BPD, 3% vs 8%, $p<0.01$.

Discussion:

The SUPPORT trial is the first ~~large~~ multicenter trial~~study~~ to ~~prospectively~~ compare early CPAP~~,~~ with early surfactant given within an hour of life in ~~to a large group of~~ ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[14~~14~~] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation~~,~~ and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our

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methodology of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.**8 We believed that testing this complete approach would be provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. As with any prospective randomized trial differences may exist in baseline characteristics and we noted more males in our Surfactant arm although this difference failed to reach significance. We believed that the clinical significance of this difference was relevant and chose to further adjust our results for gender which resulted in a loss of significance for our primary outcome variable using the definition of BPD as requiring oxygen at 36 weeks age. However we also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The group of 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were

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adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP with~~and~~ a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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To: Gantz, Marie
Cc: Rich, Wade; Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks, and 26 to 27 6/7th weeks. Infants randomized to CPAP were treated with CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1317 infants from February 2005 to February 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.001$). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.015$). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, ($p<0.001$). There were no differences between the groups for airleaks including penumothoraces. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, $p=0.03$).

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or survival with BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22

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months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC) and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI).[13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age, and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation

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or CPAP received 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group, most occurring within the first 2 days (9.1% vs 3.0%, p=.001), consistent with the findings of an earlier meta analyses4 and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this study was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision has been made to provide full resuscitation without known malformations, and for whom parental consent had been obtained. The infants were randomized to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery . While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50% , a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for Intubation for the CPAP infants. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1516]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses was a logistic regression analysis of the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks and on the percent infants who survive without neurodevelopmental sequelae at 2 years. Adjustment was performed as pre-specified for gestational age, center and familial clustering. A two-sided P value of less than 0.05 was considered to statistically significant. An independent data safety monitoring committee reviewed the interim results, including those concerning adverse outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

The study was approved by Human Subjects Committees at all participating sites and RTI, the data center, and parental consent was required before delivery.

Results:

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There were 1317 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009. The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Early Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight Apgar scores or race between the 2 groups, although there were more boys in the CPAP arm, p=.056. The Surfactant group received significantly more epinephrine in the delivery room and had a higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p < 0.05$, when adjusted for gestational age, center and familial clustering as prespecified). There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, p=.27. Using the Physiologic Definition for BPD there was a non-significant decrease in the occurrence of BPD in the CPAP group (40% vs 41%, p=.96), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=.32).

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.0149). We prospectively recorded air leaks in the first 14 days and there were no differences between the groups, and no differences for medical or surgical NEC, PDA requiring surgery, severe IVH or airleaks during the hospital stay. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs13%, p=0.0004). Death during the hospitalization was 4% lower for the CPAP group overall, and was significantly lower in the CPAP arm the 24 to 25 week strata even after adjustment which included gender.

Strata Results: 24 – 25 weeks Gestation

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There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group. The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality 24% vs 32%, p=0.03. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, p=0.02 for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p<0.01, lesser days of mechanical ventilation, 10.7 vs 14.2, p<0.01, and less postnatal steroids for BPD, 3% vs 8%, p<0.01.

Discussion:

The SUPPORT trial is the first large multicenter study to prospectively compare early CPAP, with early surfactant given within an hour of life to a large group of ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

Our study differs from the recently reported COIN trial[14] in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation, and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our methodology of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.** We believed that testing this complete approach would be provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. As with any prospective randomized trial differences may exist in baseline characteristics and we noted more males in our Surfactant arm although this difference failed to reach significance. We believed that the clinical significance of this difference was relevant and chose to further adjust our results for gender which resulted in a loss of significance for our primary outcome variable

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using the definition of BPD as requiring oxygen at 36 weeks age. However we also noted a very significant 8% reduction in death in our 24 to 25 week strata, resulting in a number needed to treat of 12.5 for each additional survivor. The 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O compared to the use of early surfactant.

The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP and a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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Tables

Table 1. Demographic Description of Overall Study Population

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300

Table 2. Neonatal Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9797
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	99.9 ± 42.6	100.5 ± 39.4	0.8210
Days on supplemental oxygen (survivors only)	53.9 ± 37.2	57.4 ± 37.0	0.1138
Days on mechanical vent (HFV & CV) (survivors only)	19.0 ± 22.8	22.0 ± 24.8	0.0392*
Days on CPAP (survivors only)	16.1 ± 13.2	16.0 ± 14.6	0.9229
Discharge on oxygen	22% (120/547)	24% (121/514)	0.5334
Alive and off MV (HFV/CV) at 7 days	55% (362/654)	49% (316/650)	0.0149*
Any air leak in first 14 days	7% (44/664)	8% (49/652)	0.5293
Medical or surgical NEC	13% (83/655)	10% (62/634)	0.1004
PDA requiring surgery	11% (73/654)	11% (68/634)	0.8019
IVH grade 3-4	15% (95/644)	13% (80/627)	0.3027
PVL	4% (28/644)	4% (27/627)	0.9709
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0004*

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Table 3. 24 to 25 weeks Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Birth weight (grams)	718.4 ± 124.7	698.4 ± 139.5	0.0718
Gestational age at birth (weeks)	25.1 ± 0.5	25.0 ± 0.5	0.1110
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.0 ± 47.4	118.6 ± 39.6	0.7514
Days on supplemental oxygen (survivors only)	75.7 ± 34.1	76.8 ± 33.1	0.7500
Days on mechanical vent (HFV & CV) (survivors only)	32.1 ± 26.6	35.8 ± 27.8	0.1672
Days on CPAP (survivors only)	18.6 ± 13.9	17.7 ± 15.5	0.5496
Discharge on oxygen	32% (68/212)	31% (57/185)	0.7867
Any air leak in first 14 days	8% (22/285)	10% (28/280)	0.3399
Medical or surgical NEC	15% (42/279)	13% (34/267)	0.4338
PDA requiring surgery	16% (46/279)	18% (47/267)	0.7289
IVH grade 3-4	19% (53/273)	19% (50/265)	0.8722
PVL	6% (16/273)	6% (15/265)	0.9206
Intubated in DR	51% (144/283)	94% (263/280)	<0.0001*
Any intubation	93% (265/284)	100% (279/280)	<0.0001*

Table 4. 25 to 26 weeks Strata

Characteristic	CPAP (N=379)	Surfactant (N=372)	Unadjusted P-value
Death in the first week	4% (15/379)	3% (10/372)	0.3322
Death at any time while hospitalized	11% (41/379)	10% (37/372)	0.6954
Total LOS any hospital (survivors only)	87.2 ± 33.6	90.2 ± 35.4	0.2515
Days on supplemental oxygen (survivors only)	39.8 ± 31.9	46.5 ± 34.6	0.0097*
Days on mechanical vent (HFV & CV) (survivors only)	10.7 ± 14.9	14.2 ± 19.0	0.0068*
Days on CPAP (survivors only)	14.5 ± 12.5	15.1 ± 14.0	0.5878
Discharge on oxygen	16% (52/335)	19% (64/329)	0.1823
Any air leak in first 14 days	6% (22/379)	6% (21/372)	0.9250
Medical or surgical NEC	11% (41/376)	8% (28/367)	0.1241
PDA requiring surgery	7% (27/375)	6% (21/367)	0.4132
IVH grade 3-4	11% (42/371)	8% (30/362)	0.1677
PVL	3% (12/371)	3% (12/362)	0.9512
Postnatal steroids for BPD	3% (11/374)	8% (29/366)	0.0027*

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Characteristic	CPAP (N=379)	Surfactant (N=372)	Unadjusted P-value
Intubated in DR	22% (82/376)	93% (345/371)	<0.0001*
Any intubation	75% (284/379)	100% (371/372)	<0.0001*

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From: Finer, Neil
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Abhik Das; Rich, Wade; Wally Carlo; Zaterka-Baxter, Kristin
Subject: Re: SUPPORT missing data updates
Date: Monday, September 28, 2009 11:21:42 AM

Hi Marie
Remind me from our past conversations as to how many of the infants with incomplete eye diagnoses have been seen in follow-up, or more importantly lost to follow-up
For how many infants did follow-up provide additional data for the eye outcome?
Of the 57 infants with the last exam in Zone 1 or 2, for those who have not yet been seen at follow-up can we call these families regarding whether they had any further eye exams- Have we done this??
Thanks
Neil

On 9/25/09 1:52 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

55 cases with vessels in zone 2

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT
Date: Monday, September 28, 2009 4:13:20 PM
Attachments: SUPPORT BPD queries Center 19 (07-24-09) MG notes.rtf

Attached is the list of Duke BPD queries with my comments. Some cases have been resolved and some have not. In cases where there are still inconsistencies, I have highlighted my comments in yellow. Note that there are a few cases where the infant's status on the NG03 and SUPP09 are inconsistent with each other in terms of whether the infant was transferred.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
919-254-8255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 28, 2009 9:14 AM
To: Gantz, Marie
Subject: FW: SUPPORT

Marie
Are these the ones that haven't been answered yet?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:53 PM
To: Ronald N Goldberg; Ricki F Goldstein; Michael Cotten; gloria.siaw@duke.edu
Cc: 'Gantz, Marie'
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.
19	[redacted]	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.

CENTER	NETWORK	FU_message
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution	Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6) .			MG: Per NG03 infant was in hospital at 36 weeks and status was DC home on (b) (6) SUPP09 status was DC on (b) (6) There is a SUPP11 for (b) (6)	

Center ID number=19=Duke University Network numbe (b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	?	.	.	O2	.	.	.	Y

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	N	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution	Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was in hospital at 36 weeks and status was DC home on (b) (6) Status on SUPP09 was DC on (b) (6) . The last SUPP11 is for (b) (6)	

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 19-Duke University

Query 1	Query 2	Query 3	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through 09/17/05.	Infant was hospitalized @36wks per NG03 but was not available for challenge due to TF per PHY01.		MG: Per NG03 infant was in hospital at 36 weeks and status was DC home on (b) (6) . Per SUPP09 infant was DC home on (b) (6) There is no SUPP11 for (b) (6) There is no indication that the infant was transferred other than the fact that they were not available for challenge per PHY01.

Center ID number=19=Duke University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01y1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01y1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant status was TF on (b) (6) and infant was DC home on (b) (6) . Status on SUPP09 was DC on (b) (6) There is no SUPP11 for (b) (6)

Center ID number=19=Duke University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01y1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01y1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	?	.	.	RA	.	?	.	Y

NG07 C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) 5) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant status was TF on (b) (6) and infant was DC home on (b) (6) . Status on SUPP09 was DC on (b) (6) 5. There is a SUPP11 for (b) (6)

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through 08/05/06.			MG: Per NG03 infant status was TF on(b) (6) and infant was DC home on [redacted] Status on SUPP09 was TF on(b) (6) There is a SUPP11 for(b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	O2	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	N	Infant left hospital on(b) (6) per NG03 but SUPP11 forms are only entered through 08/27/06.			MG: Per NG03 infant status was TF on(b) (6) and infant was DC home on 10/10/06. Status on SUPP09 was TF on(b) (6) There is a SUPP11 for(b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 19-Duke University

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant status was TF on (b) (6) and infant was DC home on (b) (6) Status on SUPP09 was TF on (b) (6) There is a SUPP11 for (b) (6)

Center ID number=19=Duke University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC
Y	Y	Y	Y	.	RA	O2	None	.

PH01v1 @36wks O2/RA(flow) by Nc	PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA
.	N		.	.	.	.	.	.

SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	.	.	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).			MG: NG07 snapshot now has RA by vent

Center ID number=19=Duke University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	RA	.	N	.	N

Query 1	Query 2	Query 3	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Infant was discharged on day of 36wks per NG03 but is missing 36wk snapshot on NG07.		MG: Per NG03 infant status was TF on (b) (6) and infant was DC home on (b) (6) . Status on SUPP09 was TF on (b) (6) There a SUPP11 (b) (6)

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/ Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: There is no NG03 for this infant. Status on SUPP09 was TF on (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

PH01v1 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	RA	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/ Center notes
N	.	N	Infant left hospital on (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant status was DC home on (b) (6). Status on SUPP09 was TF on (b) (6). There is a SUPP11 for (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	N	N	Y	RA	RA	N	Y	N	N

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SUPPORT BPD Queries for Center 19-Duke University

Query 1	Query 2	Query 3	Query resolution - Center notes
NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).	RA by NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).		MG: RA by NC/CPAP/vent per NG07, RA by NC flow 0.1 per SUPP11

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC
.	.	.	.	.	.	.	.	.

PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA
.	.		.	N	Y	.	O2&RA	O2

SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution - Center notes
Y	.	Y	N	O2 by NC @status is inconsistent across forms (NG07/SUPP11).			MG: NG07 has FiO2=.27. SUPP11 has O2 by NC. If O2 on that day was by NC only (not by vent or CPAP), then NG07 Q6 Highest FiO2 should be blank and Q7 Supplemental O2 by NC should be 'Y.'

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution - Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through 09/05/07.			MG: Per NG03 infant was in hospital at 36 weeks and status was DC home on (b) (6). Status on SUPP09 was DC on (b) (6) SUPP11s are only entered through (b) (6)

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07 C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution	Enter notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was hospitalized at 36 weeks and was still in hospital at 120 days. SUPP09 status is DC home on (b) (6) . There is a SUPP11 for 36 week date (b) (6)	

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution	Enter notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was in hospital at 36 weeks and status was DC home on (b) (6) . Status on SUPP09 was DC on (b) (6) There is a SUPP11 for (b) (6)	

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 19-Duke University

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was in hospital at 36 weeks and was still hospitalized at 120 days. Status on SUPP09 was TF on (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was in hospital at 36 weeks and was DC home on (b) (6) Status on SUPP09 was TF on (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was in hospital at 36 weeks and was DC home on (b) (6) Status on SUPP09 was DC on (b) (6) There is a SUPP11 for (b) (6)

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/ center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was TF on (b) (6) and DC home on (b) (6) Status on SUPP09 was TF on (b) (6) . There is a SUPP11 for (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/ center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was TF on (b) (6) and DC home on (b) (6) Status on SUPP09 was TF on (b) (6) There is a SUPP11 for (b) (6)

Center ID number=19=Duke University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	Y	Y	Y	O2	RA	.	Y	Y	N

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SUPPORT BPD Queries for Center 19-Duke University

Query 1	Query 2	Query 3	Query resolution Center notes
Number of days on vent/CPAP @status per NG07 (b) (6) is greater than DOL @status per NG03 (b) (6)	Any O2/RA @status is inconsistent across forms (NG07/SUPP11).	RA by NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).	MG: Days on vent/CPAP at status is now (b) (6) Infant on O2 by NC and by CPAP at status per SUPP11 but on RA by NC/CPAP/vent per NG07. NG07 should capture maximum support for the day.

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	N	Y	.	RA	O2	Y	.	N	N

Query 1	Query 2	Query 3	Query resolution Center notes
Any O2/RA @status is inconsistent across forms (NG07/SUPP11).	RA by NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).		MG: NG07 has FiO2=.23. SUPP11 has O2 by NC. If O2 on that day was by NC only (not by vent or CPAP), then NG07 Q6 Highest FiO2 should be blank and Q7 Supplemental O2 by NC should be 'Y.'

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was TF on (b) (6) and DC home on (b) (6) Status on SUPP09 was TF on (b) (6) There is a SUPP11 for (b) (6)

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SUPPORT BPD Queries for Center 19-Duke University

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	Y	.	Y	.	.	RA	.	.	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution / Center notes
.	.	.	Infant was hospitalized @36wks per NG03 but no SUPP11 forms have been entered.			MG: Per NG03 infant was in hospital at 36 weeks and was still hospitalized at 120 days. Status on SUPP09 was in hospital (b) (6) . SUPP11s have only been entered through (b) (6)

Center ID number=19=Duke University Network number=(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	RA	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution / Center notes
N	.	N	Infant left hospital on (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			MG: Per NG03 infant was TF on (b) (6) and DC home on (b) (6) Status on SUPP09 was TF on (b) (6) There is a SUPP11 for (b) (6) .

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From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kimberley A Fisher; Ronald N Goldberg
Subject: Re: SUPPORT!!!
Date: Monday, September 28, 2009 3:11:05 PM

---

thanks Rose.

I am optimistic that our ROP outcomes can be settled with tomorrow's visit.

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
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Durham, NC 27710
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Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
09/28/2009 03:06 PM

To
"'Finer, Neil'" <nfiner@ucsd.edu>, "'Sood, Beena'" <bsood@med.wayne.edu>, "'Susie Buchter'" <Susie.Buchter@oz.ped.emory.edu>, "'Finer, Neil'" <nfiner@ucsd.edu>, " (Luc.Brion@UTSouthwestern.edu)" <Luc.Brion@UTSouthwestern.edu>, " (rohls@unm.edu)" <rohls@unm.edu>, "aaf2@po.cwru.edu" <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>, "alaptook@WIHRI.org" <alaptook@WIHRI.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, Dennis Wallace <dwallace@rti.org>, Ed Bell <Edward-bell@uiowa.edu>, Ed Donovan

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cc

"'Zaterka-Baxter, Kristin'"
<kzaterka@rti.org>, "'Cunningham,
Meg'" <mcunningham@rti.org>,
"Archer, Stephanie (NIH/NICHD) [E]"
<archerst@mail.nih.gov>

Subject

SUPPORT!!!

There are 109 infants without an ROP outcome in the SUPPORT trial (n=1317).
We need to finalize and lock the ROP data so that the analysis can proceed.
The final date for Data Entry for SUPPORT ROP is OCTOBER 20. Please insure that you have the outcomes for your infants entered by October 20!!!

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Oxygen saturation targeting paper
Date: Monday, September 28, 2009 2:38:14 PM

From: Gantz, Marie
Sent: Monday, September 21, 2009 4:43 PM
To: 'Finer, Neil'; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi all,

Thanks for your patience while I was away. I have made few edits and comments to the latest version of Wally's paper. Wally, you had mentioned that you were missing some outcomes (like IVH/death) and I believe those were included in tables I sent on Sept. 3 (T2S Major Outcomes - PRELIMINARY 03SEP09.doc) – let me know if you need me to resend them.

Regarding the earlier question about the numbers in figure 1 differing from the monthly report, in the monthly report "*Eligible GDB patients are those keyed in the NG02 (inborn and GA of 24 0/6 & 27 6/7) with a birth date after the first Support patient keyed for sites at each Center and not born on or between dates of Support study suspension 11/23/2005 and 2/5/2006*" while the 3546 in figure 1 are those infants who were entered on the SUPP01 screening log. I'm not sure what to do about the difference unless we add them to the number who were "eligible but consent not sought." We should also be clear in figure 1 that many more moms were screened than are reflected on the SUPP01, because only those infants who were eventually assigned a GDB number (or who were enrolled in SUPPORT) were entered into the DMS. We could reference Wade's antenatal consent paper for a more accurate estimate of how many moms were screened.

FYI, while I was gone, queries went out to the centers regarding data that differed across GDB and SUPPORT forms and that will impact the secondary outcomes (including things like IVH) to some (hopefully small) degree. We have heard back from 10 centers so far, and I will review the results of the queries as we get responses to make sure all the necessary data are cleaned. I will also re-review the BPD outcome data to see if those queries have been completely cleared up yet and I will remind centers of any outstanding queries.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 18, 2009 9:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi Wally

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I have made a few changes
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 18, 2009 1:29 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper

Dear Neil, Rose, Abhik, and Marie:

I have made several changes including:
1. Making Neil's suggestions
2. Improved Figure 2
3. Included Figure 1
4. Multiple minor changes.

I have made changes in all the numbers of the results as Abhik said they are still not final.

Enclosed is a clean draft so you can see my comments. I think we need to consider adding the ROP data if it is final before the paper is ready for submission.

I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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From: Gantz, Marie
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Rich, Wade; Wally Carlo; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates
Date: Monday, September 28, 2009 2:00:23 PM

Here is the FU window status for infants missing ROP:

Those with lowest zone of any vessels=1 at last exam (N=2)
- 2 with closed FU windows (have not looked to see if FU visit took place)

Those with lowest zone of any vessels=2 at last exam (N=55)
- 18 with closed FU windows (have not looked to see if FU visit took place)
- 7 with windows open now
- 30 with windows not opened yet

Those with lowest zone of any vessels=3 at last exam (N=52)
- 21 with closed FU windows (have not looked to see if FU visit took place)
- 4 with windows open now
- 27 with windows not opened yet

According to the SUPP10, there were 16 cases where final ROP status was obtained at the FU visit.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, September 28, 2009 11:22 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Rich, Wade; Wally Carlo; Zaterka-Baxter, Kristin
Subject: Re: SUPPORT missing data updates

Hi Marie
Remind me from our past conversations as to how many of the infants with incomplete eye diagnoses have been seen in follow-up, or more importantly lost to follow-up
For how many infants did follow-up provide additional data for the eye outcome?
Of the 57 infants with the last exam in Zone 1 or 2, for those who have not yet been seen at follow-up can we call these families regarding whether they had any further eye exams- Have we done this??
Thanks
Neil

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On 9/25/09 1:52 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

55 cases with vessels in zone 2

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From: Gantz, Marie
To: Roger Falx; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Karen Osborne RN; Bradley Yoder; Nichol Nunn
Subject: RE: SUPPORT!!!
Date: Monday, September 28, 2009 1:43:10 PM

If the data were transmitted on Thursday then we probably have it; however, our analysis datasets are only updated once a week (after the Tuesday transmissions) so that's why I did not see the new ROP data in my version of the dataset. Thanks!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
13-54-825

From: Roger Falx [mailto:Roger.Falx@hsc.utah.edu]
Sent: Monday, September 28, 2009 12:29 PM
To: Gantz, Marie; higginsr@mail.nih.gov
Cc: Karen Osborne RN; Bradley Yoder; Nichol Nunn
Subject: FW: SUPPORT!!!

See below. We will transmit it again today, in the event something prevented appropriate delivery on the first attempt.

Roger

From: Nichol Nunn
Sent: Monday, September 28, 2009 10:23 AM
To: Roger Falx
Subject: RE: SUPPORT!!!

That is most likely the case. I think I got the chart on Wednesday. But I did transmit on Thursday so I don't know why they don't have it unless they haven't looked since then. I will transmit again today.

Nichol Nunn
Data Entry Coordinator
Neonatal Research Network
University of Utah
Dept of Pediatrics, Division of Neonatology
PO Box 581289
Salt Lake City, UT 84158
Phone #(801) 213-3296

From: Roger Falx
Sent: Monday, September 28, 2009 10:20 AM
To: Nichol Nunn
Subject: FW: SUPPORT!!!

Could this be the case? If so, can we please transmit it?

Roger

From: Gantz, Marie [mgantz@rti.org]
Sent: Monday, September 28, 2009 9:43 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Karen Osborne RN; Roger Falx; Bradley Yoder
Subject: RE: SUPPORT!!!

Hi Karen,

The last exam we have for this infant was on 5/27/09 (entered into the DMS on 5/29) and the infant had not reached final ROP status. Perhaps the latest exam entered last week has not been transmitted yet?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
13-54-825

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 5:21 PM
To: 'karen.osborne@hsc.utah.edu'; 'Roger.Falx@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'
Cc: Gantz, Marie
Subject: Re: SUPPORT!!!

Marie - can you check this one?
Rosemary D. Higgins, MD
Program Scientist

From: Karen Osborne RN <Karen.Osborne@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Roger Falx <Roger.Falx@hsc.utah.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
Cc: 'Gantz, Marie' <mgantz@rti.org>
Sent: Fri Sep 25 17:15:13 2009
Subject: RE: SUPPORT!!!

Hi Rose,

The ROP final outcome on this baby was entered into the database earlier this week.

Thanks,

Karen

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 3:05 PM
To: Roger Falx; Bradley Yoder; Karen Osborne RN
Cc: 'Gantz, Marie'
Subject: SUPPORT!!!

Hi,
We are missing a few SUPPORT Primary outcomes. Please get these entered ASAP as we want to lock the database.

Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
25	(b)(6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)

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higginsr@mail.nih.gov

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Updates of tables 1-3
Date: Monday, September 28, 2009 1:12:03 PM
Attachments: tables.docx

Not sure you have seen this...

From: Das, Abhik
Sent: Tuesday, September 15, 2009 1:43 PM
To: 'Finer, Neil'; 'wacarlo@uab.edu'; 'Rich, Wade'
Cc: Gantz, Marie
Subject: RE: Updates of tables 1-3

Marie wanted me to run the adjusted analyses while she was away, and I took my own time getting to it! I also used a different modeling approach that I have not had the chance to discuss with Marie yet; so please consider these draft results (and also the explanation for why some of the p values differ slightly from what you heard during our meeting in Rockville).

In doing adjusted analyses, my goal was to do this in a way that accomplishes two objectives:

1. Produce adjusted relative risks (and associated confidence intervals) instead of adjusted odds ratios, since the former make more sense interpreting in the context of a clinical trial.
2. Adjust for center, a stratification variable, as a traditional fixed effect (which means that we allow each center to have a different mean prevalence rate for the outcome), instead of treating it as a random effect (which indirectly adjusts for center effects by allowing babies from the same center to have outcomes more similar than those for babies across different centers).

After some experimentation, I settled on a generalized estimating equation (GEE) model that uses robust Poisson regression to produce adjusted relative risks, with center treated as a traditional fixed effect. In order to make this modeling approach computationally feasible, for most analyses I had to combine the data from 2 centers with less than 10 babies each, with their nearest larger center (Wake Forest was combined with Duke and Rochester with Yale). For the outcome of death by 36 weeks, I also had to combine Miami (<20 babies) with Emory.

The results, both for the design adjusted models (adjusting for GA strata, center and familial clustering) and for design + gender adjusted models, appear in the attached.

Please let me know if you have any questions.

Thanks

Abhik

From: Gantz, Marie

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Sent: Friday, September 04, 2009 10:55 PM
To: 'Finer, Neil'; wacarlo@uab.edu; 'Rich, Wade'
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: Updates of tables 1-3

Attached are updates of tables 1-3 that we went over at our meeting this week. These versions were run on our most recent data. Adjusted p-values for the BPD and death outcomes will follow.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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SUPPORT Trial Draft Primary Analysis (Based on Preliminary Data)

All Study Subjects: Ventilation Arm

Characteristic	CPAP (N=664)	Surfactant (N=652)	Design Adjusted[1]		Design + Gender Adjusted[2]	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	14% (94/664)	17% (114/652)	0.8 (0.63, 1.03)	0.09	0.81 (0.63, 1.04)	0.1
Death (all)	16% (109/664)	19% (127/652)	0.84 (0.67, 1.06)	0.14	0.85 (0.68, 1.07)	0.17
BPD (physiologic definition)	40% (226/570)	41% (221/538)	1.0 (0.87, 1.14)	0.96	1.0 (0.88, 1.15)	0.96
BPD (physiologic definition) or death by 36 weeks PMA	48% (320/664)	51% (335/652)	0.95 (0.86, 1.05)	0.32	0.95 (0.86, 1.06)	0.38
BPD (supplemental O2)	40% (227/570)	44% (238/538)	0.93 (0.82, 1.06)	0.27	0.94 (0.83, 1.07)	0.35
BPD (supplemental O2) or death by 36 weeks PMA	48% (321/664)	54% (352/652)	0.91 (0.82, 1.0)	0.05	0.91 (0.83, 1.01)	0.08

1 Adjusted for GA strata, center and familial clustering
2 Adjusted for GA strata, center , familial clustering and gender

All Study Subjects: Oxygenation Arm

Characteristic	High SpO2 (N=661)	Low SpO2 (N=655)	Design Adjusted		Design + Gender Adjusted	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	14% (94/661)	17% (114/655)	0.79 (0.62, 1.02)	0.07	0.78 (0.61, 1.0)	0.05
Death (all)	16% (106/661)	20% (130/655)	0.78 (0.62,0.99)	0.04	0.77 (0.61,0.97)	0.03
BPD (physiologic definition)	42% (239/567)	38% (208/541)	1.08 (0.95, 1.24)	0.25	1.08 (0.94, 1.23)	0.28
BPD (physiologic definition) or death by 36 weeks PMA	50% (333/661)	49% (322/655)	1.01 (0.91, 1.12)	0.91	1.0 (0.9, 1.11)	0.96
BPD (supplemental O2)	46% (262/567)	38% (203/541)	1.22 (1.07, 1.39)	0.003	1.21 (1.06, 1.38)	0.004
BPD (supplemental O2) or death by 36 weeks PMA	54% (356/661)	48% (317/655)	1.09 (0.99, 1.21)	0.09	1.08 (0.98, 1.2)	0.11

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GA = 24-25 weeks: Ventilation Arm

Characteristic	CPAP (N=285)	Surfactant (N=280)	Design Adjusted		Design + Gender Adjusted	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	20% (57/285)	29% (82/280)	0.68 (0.5, 0.92)	0.01	0.69 (0.51, 0.93)	0.01
Death (all)	24% (68/285)	32% (90/280)	0.74 (0.57, 0.98)	0.03	0.75 (0.57, 0.99)	0.04
BPD (physiologic definition)	55% (126/228)	55% (108/198)	1.07 (0.91, 1.26)	0.39	1.08 (0.92, 1.27)	0.34
BPD (physiologic definition) or death by 36 weeks PMA	64% (183/285)	68% (190/280)	0.96 (0.86, 1.08)	0.52	0.97 (0.86, 1.09)	0.57
BPD (supplemental O2)	54% (122/228)	54% (107/198)	1.05 (0.89, 1.23)	0.57	1.06 (0.9, 1.25)	0.46
BPD (supplemental O2) or death by 36 weeks PMA	63% (179/285)	68% (189/280)	0.94 (0.84, 1.06)	0.32	0.95 (0.84, 1.07)	0.39

GA = 24-25 weeks: Oxygenation Arm

Characteristic	High SpO2 (N=287)	Low SpO2 (N=278)	Design Adjusted		Design + Gender Adjusted	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	22% (64/287)	27% (75/278)	0.8 (0.59, 1.09)	0.16	0.79 (0.58, 1.07)	0.13
Death (all)	25% (73/287)	31% (85/278)	0.81 (0.62,1.07)	0.14	0.79 (0.6, 1.05)	0.11
BPD (physiologic definition)	57% (128/223)	52% (106/203)	1.1 (0.93, 1.29)	0.26	1.09 (0.92, 1.27)	0.32
BPD (physiologic definition) or death by 36 weeks PMA	67% (192/287)	65% (181/278)	1.02 (0.91, 1.14)	0.76	1.01 (0.9, 1.13)	0.86
BPD (supplemental O2)	57% (127/223)	50% (102/203)	1.13 (0.96, 1.33)	0.14	1.11 (0.94, 1.31)	0.21
BPD (supplemental O2) or death by 36 weeks PMA	67% (191/287)	64% (177/278)	1.03 (0.92, 1.16)	0.6	1.02 (0.91, 1.15)	0.75

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GA = 26-27 weeks: Ventilation Arm

Characteristic	CPAP (N=379)	Surfactant (N=372)	Design Adjusted		Design & Gender Adjusted	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	10% 37/379)	9% (32/372)	1.12 (0.72, 1.74)	0.63	1.13 (0.72, 1.76)	0.6
Death (all)	11% (41/379)	10% (37/372)	1.08 (0.71, 1.64)	0.72	1.09 (0.72, 1.65)	0.69
BPD (physiologic definition)	29% (100/342)	33% (113/340)	0.92 (0.74, 1.14)	0.45	0.92 (0.74, 1.15)	0.48
BPD (physiologic definition) or death by 36 weeks PMA	36% (137/379)	39% (145/372)	0.93 (0.77, 1.12)	0.45	0.94 (0.78, 1.13)	0.5
BPD (supplemental O2)	31% (105/342)	39% (131/340)	0.83 (0.68, 1.01)	0.06	0.84 (0.69, 1.02)	0.08
BPD (supplemental O2) or death by 36 weeks PMA	37% (142/379)	44% (163/372)	0.87 (0.73, 1.02)	0.09	0.87 (0.74, 1.03)	0.11

GA = 26-27 weeks: Oxygenation Arm

Characteristic	High SpO2 (N=374)	Low SpO2 (N=377)	Design Adjusted		Design & Gender Adjusted	
			Relative Risk (95%CI)	p value	Relative Risk (95%CI)	p value
Death by 36 weeks PMA	8% (30/374)	10% (39/377)	0.77 (0.49, 1.2)	0.24	0.77 (0.49, 1.2)	0.24
Death (all)	9% (33/374)	12% (45/377)	0.73 (0.48,1.1)	0.13	0.73 (0.48, 1.1)	0.13
BPD (physiologic definition)	32% (111/344)	30% (102/338)	1.06 (0.86, 1.32)	0.57	1.07 (0.86, 1.32)	0.56
BPD (physiologic definition) or death by 36 weeks PMA	38% (141/374)	37% (141/377)	0.99 (0.82, 1.19)	0.92	0.99 (0.83, 1.19)	0.93
BPD (supplemental O2)	39% (135/344)	30% (101/338)	1.31 (1.07, 1.6)	0.01	1.31 (1.08, 1.6)	0.01
BPD (supplemental O2) or death by 36 weeks PMA	44% (165/374)	37% (140/377)	1.17 (0.99, 1.38)	0.07	1.17 (0.99, 1.38)	0.07

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From: Das, Abhik
To: Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper
Date: Monday, September 28, 2009 1:04:38 PM
Attachments: Oxygen Saturation Targeting 9 18 09Rev NF MG AD.doc

Hello All:

Please see my belated comments and suggested changes for this paper.

Thanks

Abhik

From: Gantz, Marie
Sent: Monday, September 21, 2009 4:43 PM
To: 'Finer, Neil'; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi all,

Thanks for your patience while I was away. I have made few edits and comments to the latest version of Wally's paper. Wally, you had mentioned that you were missing some outcomes (like IVH/death) and I believe those were included in tables I sent on Sept. 3 (T2S Major Outcomes - PRELIMINARY 03SEP09.doc) – let me know if you need me to resend them.

Regarding the earlier question about the numbers in figure 1 differing from the monthly report, in the monthly report "*Eligible GDB patients are those keyed in the NG02 (inborn and GA of 24 0/6 & 27 6/7) with a birth date after the first Support patient keyed for sites at each Center and not born on or between dates of Support study suspension 11/23/2005 and 2/5/2006*" while the 3546 in figure 1 are those infants who were entered on the SUPP01 screening log. I'm not sure what to do about the difference unless we add them to the number who were "eligible but consent not sought." We should also be clear in figure 1 that many more moms were screened than are reflected on the SUPP01, because only those infants who were eventually assigned a GDB number (or who were enrolled in SUPPORT) were entered into the DMS. We could reference Wade's antenatal consent paper for a more accurate estimate of how many moms were screened.

FYI, while I was gone, queries went out to the centers regarding data that differed across GDB and SUPPORT forms and that will impact the secondary outcomes (including things like IVH) to some (hopefully small) degree. We have heard back from 10 centers so far, and I will review the results of the queries as we get responses to make sure all the necessary data are cleaned. I will also re-review the BPD outcome data to see if those queries have been completely cleared up yet and I will remind centers of any outstanding queries.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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828-251-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 18, 2009 9:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi Wally
I have made a few changes
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 18, 2009 1:29 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper

Dear Neil, Rose, Abhik, and Marie:

I have made several changes including:
1. Making Neil's suggestions
2. Improved Figure 2
3. Included Figure 1
4. Multiple minor changes.

I have made changes in all the numbers of the results as Abhik said they are still not final.

Enclosed is a clean draft so you can see my comments. I think we need to consider adding the ROP data if it is final before the paper is ready for submission.

I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
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9/18/09
4.0

The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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9/18/09
4.0

Word count:

Abstract: 93

Manuscript: 1921

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the NICHD Neonatal Research Network (NRN) were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Comment [AD1]: Since we are not reporting ROP outcomes and would emphasize morality differences, I think we need to set the stage for doing that in the Intro itself, along the lines suggested in Neil's email dated 9/1/09.

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to also increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80mmHg.[14]

The recent introduction of pulse oximeters into the neonatal intensive care units, have allowed clinicians to utilize oxygen saturations to target oxygenation in premature infants. A survey study of 144 neonatal intensive care units conducted in 2001, revealed that the average lower limit of target oxygen saturations was 90% and the upper limit was 96%.[5] In recent years, the use of high saturation targets has been associated with the increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%) or $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%).[5] Recent studies suggest that oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy. In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe

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retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, in these studies, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and ventilation strategy. ~~: testing~~ The oxygen saturation arm tested the effect of a lower oxygen saturation target range (85-89%) ~~as~~ compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. ~~The factorial design allowed comparison~~The ventilation arm of this factorial design trial also allowed us to simultaneously test~~ed~~ the effect of ~~of~~ prophylactic/early surfactant versus continuous positive airway pressure~~: thus, controlling for the approach to ventilatory support~~ on bronchopulmonary dysplasia or death at 36 weeks postmenstrual age (results published elsewhere). Note that the factorial nature of the trial design effectively controlled for ventilator approaches in the oxygen saturation arm of this trial, which is the subject of this report.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age, without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiple births were randomized to the same arm of the trial.

Enrollment and treatment

~~Infants~~ Deliveries were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). ~~Infants~~ They were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95%. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, with an offset of 3% as previously used to separate oxygen saturations in premature infants.[20] ~~Participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy.~~ The oxygen saturation values displayed reverted to actual values when less than 84~~5~~% or greater than 96~~5~~%. Oxygen saturation targeting with the altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximetry. Adjustments in supplemental oxygen to target

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oxygen saturations were performed by the clinicians, not by the research staff. For the ventilation arm of this 2 by 2 factorial design trial (results reported elsewhere), participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy.

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge or 120 days postnatal age whichever occurred first. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Outcomes included predefined clinical diagnoses and potential adverse events.

Comment [MG2]: We are also including treatment with Avastin, correct?

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a ~~logistic regression~~ generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing ~~analysis of the percentages of~~incidence rates for infants in each treatment group (lower versus higher oxygen saturations) who developed the primary outcome. The model

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produces relative risk estimates adjusted for stratification by center and gestational age, and for the familial clustering induced by randomization of multiple births to the same treatment.

An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll ~~1312~~ 1310 infants for 80% power to detect a 10% difference in outcome assuming ~~and~~ a baseline estimated rate of ~~45~~50% of death/threshold retinopathy/surgery. This sample size estimate included ~~, based on~~ an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. While these sample size calculations allowed for the testing of two co-primary outcomes for the two intervention arms (oxygenation and ventilation) of this 2 by 2 factorial trial, t~~T~~he trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted ~~by~~ at RTI International, the independent ~~d~~Data Coordinating ~~c~~Center for the NRN. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent data safety and monitoring committee appointed by the Director of the NICHD reviewed the primary outcomes, adverse events, and other interim results at ~**25%, 50%, and 75%** of planned enrollment. Lan-DeMets spending functions with Pocock (O'Brien-Fleming) boundaries were used to develop stopping rules for interim safety (efficacy) monitoring. Safety outcomes monitored included death, …, and a combination of any of the above events.

Comment [MG3]: This is what is listed on clinicaltrials.gov

Comment [MG4]: The final DSMC review will take place on November 4 to review 100% of the BPD/death data and as much of the ROP data as we have at that time.

RESULTS

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1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily stopped by the Data Safety and Monitoring Committee (DSMC) because of concerns regarding compliance with oxygen saturation targets. Separate of analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns, and trial enrollment resumed upon DSMC approval. The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The Data Safety and Monitoring Committee masked interim analyses for safety were made available to the investigators after enrollment was completed. There had been a trend for increased mortality in one of the treatment groups that had not reached the stopping boundary. The principal investigator and ~~data center~~DCC staff then undertook a more detailed safety analysis to evaluate potential adverse outcomes without unblinding the retinopathy outcome data. This manuscript reports the hospital outcomes. Retinopathy and 18-22 month follow up outcomes will be reported later.

Mortality at any time during hospitalization occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (adjusted RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed within both gestational age groups used for stratification. Mortality in the first and second weeks after birth was comparable in the two treatment groups (Table 2). Other prespecified major outcomes were comparable between the two treatment groups (Table 2).

Comment [AD5]: Is it just enrollment, or when all babies had reached status, as defined in the GDB (death, discharge, transfer or 120 days of age) ? Will we get into trouble for sharing such data with the investigators before all primary outcomes were available?

Comment [AD6]: I think we can make this stronger – the data is not all available and the investigators have not even seen the available data by group – correct?

Comment [AD7]: In order for NEJM to consider this, I think the rationale needs to be strengthened here along the following lines:
We performed a detailed safety analysis which uncovered clinically and statistically significant trends with respect to mortality. While acknowledging that the designated primary outcome for this trial is death or ROP, since death is the ultimate safety outcome, we decided not to wait for incoming ROP outcome data (which will take substantially more time to collect and QC) and report the mortality findings to the practicing neonatal community while the ROP data accumulates.

Comment [AD8]: Are we also reporting gender adjusted results?

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The median oxygen saturation of both groups differed substantially but, as expected, there was some overlap (Figure 2). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ as well.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite notw being based on randomized controlled trials and limited evidence of safety, lower oxygen saturation targeting has become been the recommendedincreasingly adopted by units and physicians who are desirous of decreasing significant retinopathy of prematurity. In the current trial, we however observed that lower oxygen saturation targeting (85-89%) resulted in an increased risk of mortality.

This trial was not prospectively powered for a difference in mortality only between the two oxygen saturation groups and, thus, the results should be viewed with caution. However, this is the largest completed prospective multi-center randomized trial to test the effect of lower versus higher oxygen saturation targeting and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of

Comment [MG9]: Although death was not the pre-specified primary outcome, the fact that the study was not specifically powered to detect a difference in death rate should not in itself lead us to be cautious about the findings. Recall that the study was powered conservatively for an outcome rate of 50%. It turned out that we also had the power to detect a difference in death rates of 16% vs. 20%.

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any previous trials of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction among the outcomes reported in this paper. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence compared to randomized controlled trials. It is interesting and worrisome that the combined risk difference observed in the 1950s was a 4.9% increase in mortality in the oxygen restricted group, which is very similar to the 4% mortality increase in the lower targeted SpO2 group that was observed in our trial. (Ref 1).

Restriction of oxygenation in previous randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group. Mortality in the current trial did not differ by 7 or 14 days. Therefore, we surmise that the lower target of oxygen saturations rather than the postnatal age of the intervention is related to the adverse outcome.

There are several ongoing trials across the world that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[1] At the present time, it is important that these trials continue. and it will be important that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85

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to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range for extremely premature babies such as those tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no.(%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Adjusted Relative Risk[1] (95% CI)
Death before discharge	130/655 (20)	106/661 (16)	
Death by 7 days	41/655 (6)	38/661 (6)	
Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	

Formatted: Superscript

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Pneumothorax – no. (%)	48/655 (7)	43/661 (7)
Any air leaks – no. (%)	50/655 (8)	43/661 (7)
Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

1 Adjusted for stratification factors (study center and GA group), as well as familial clustering

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

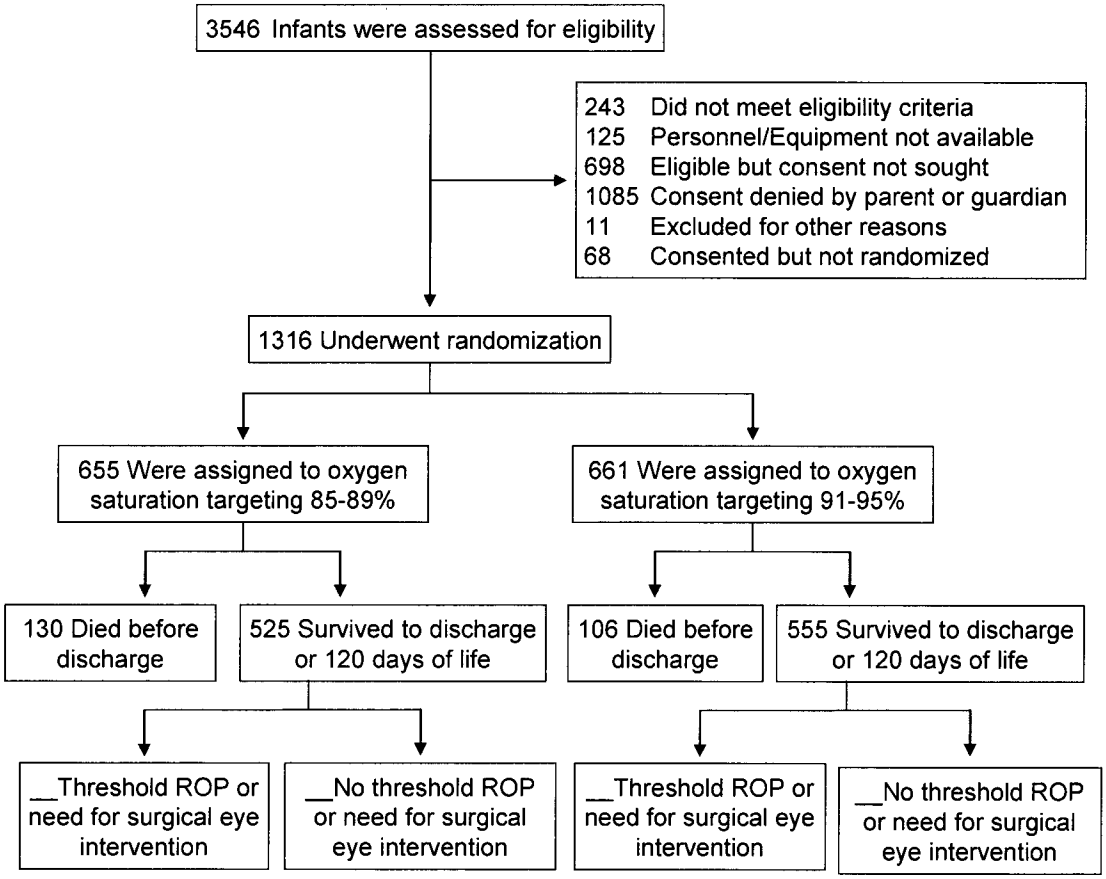

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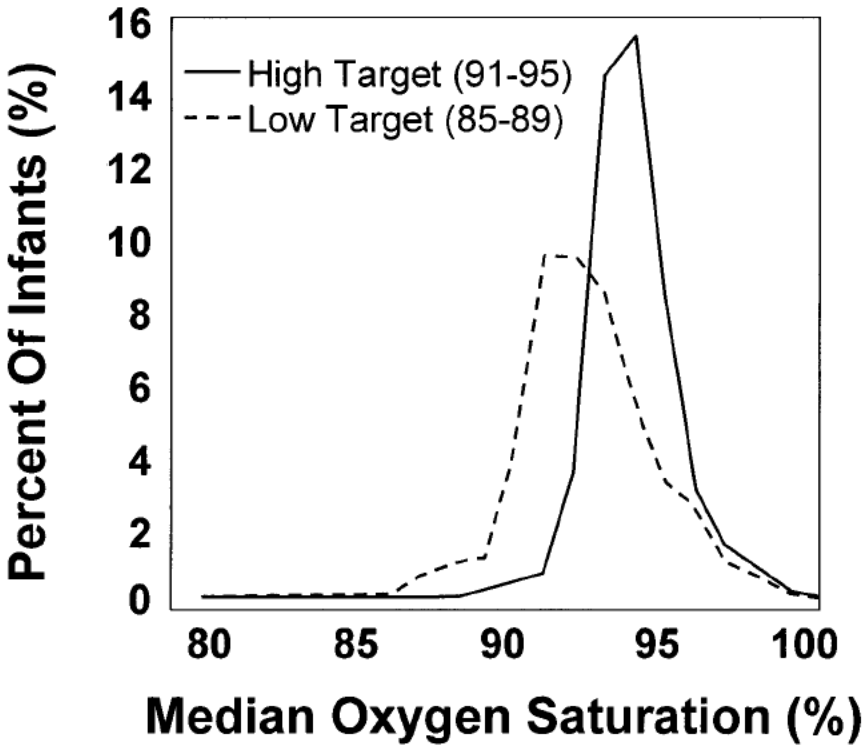
Figure 2



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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie
Subject: FW: Duke Site Visit
Date: Monday, September 28, 2009 11:20:35 AM
Attachments: (b) (6) [redacted]

Sorry for the huge email but wanted to give you a preview of the data for Duke; I will have all these in hard copy and flagged per form number.
Thanks,
Kris

From: Pickett, James
Sent: Monday, September 28, 2009 10:35 AM
To: Zaterka-Baxter, Kristin
Subject: RE: Duke Site Visit

Here are the forms, working on the audit trail and outstanding edits (this won't take long).

J

From: Zaterka-Baxter, Kristin
Sent: Thursday, September 24, 2009 11:49 AM
To: Pickett, James
Subject: Duke Site Visit
Importance: High

Hi,

We need forms:

Supp02
Supp03
Supp04
Supp05
Supp10
Supp11
NG02
NG03
NG03E (if any)
NG07
PHY01/02 (if any)

IDs

CENTER	NETWORK	DOB
19	(b) (6) [redacted]	05/28/2005
19	[redacted]	09/07/2005
19	[redacted]	08/17/2006

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19	(b) (6)	10/14/2006
19		05/21/2007
19		10/27/2007
19		06/04/2008
19		12/22/2008
19		01/18/2009
19		03/26/2007

We also need any Support outstanding edits and a DMS audit trail report (if possible of recent changes to these data)

Thanks
Kris

Kris Zaterka-Baxter
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(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
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Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **14:05**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **2**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **1**

   1= Blue 2= Orange

Initials of person completing this form: **KRF**

SUPP02 Form Completion Date: **08/30/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:
   a. Date: (b) (6) (Month Day Year) b. Time: 14:07 (Hour Min)
2. Was CPAP initiated in the DR? N
   If Yes, Date and time of CPAP initiation:
   a. Date: (Month Day Year) b. Time: (Hour Min)
   c. Device:

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)
3. Was positive pressure ventilation (PPV) initiated in the DR? Y
4. Was positive and expiratory pressure (PEEP) used in the DR? Y
   If Yes,
   a. Maximum PEEP: **
5. Was intubation attempted in the DR? Y
   If Yes, was the intubation successful? Y
6. Indication for intubation: 2

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,
   a. Low HR? Y
   b. Poor color? N
   c. Apnea? Y
   d. Other? N
   If Other specify:

   If (3) Other, specify:
7. Did the infant receive surfactant in the DR? Y
   If Yes, Date and time of administration:
   a. Date: (b) (6) (Month Day Year) b. Time: 14:14 (Hour Min)
   c. Type: 1

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

8. Was active resuscitation required? **N**

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: **1**

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: **KRF**

SUPP03 Form Completion Date: **01/18/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 14:30 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 091

4. FiO2: 0.30

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 15:15 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.30

   e. pCO2: 047

   f. pO2: 107

   g. FiO2: 0.21

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 14:10 (Hour Min)

   c. Serial number: 316774

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year

b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	01:22	1
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KRF

SUPP04 Form Completion Date: 12/10/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 01 2. Date: 05/28/2005

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**:**						
2. 16:00	17:20	7.17	070	063	0.35	1	2
3. 23:59	21:20	7.19	059	050	0.25	1	2

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 02 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:45	7.28	046	077	0.21	1	2
2. 16:00	14:00	7.25	053	063	0.21	1	2
3. 23:59	20:25	7.26	052	051	0.21	1	2

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 03 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	09:04	7.35	037	073	0.21	1	2
2. 16:00	14:28	7.26	050	062	0.21	1	2
3. 23:59	20:55	7.29	049	068	0.21	1	2

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM (b) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 04 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	07:45	7.36	035	066	0.25	1	2
2. 16:00	13:45	7.32	040	062	0.24	1	2
3. 23:59	18:30	7.25	045	057	0.24	1	4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day?	Y
a. If Yes, Record the time of intubation	17:45 (hh:mm)
b. If Yes, Type of extubation: (1= Planned 2= Accidental)	1
c. If Yes, Record the following prior to extubation	
1. pH	*.**
2. PCO2	***
3. FiO2	*.**
4. Saturation	***
3. Was a replacement study oximeter placed on this infant on this day?	N
If Yes,	
a. Serial number:	
Initials of person completing this form:	KRF
SUPP05 Form Completion Date:	10/18/2005

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 05 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	03:30	7.34	036	060	0.31	1	4
2. 16:00	16:00				0.28		4
3. 23:59	23:59				0.23		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 06 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				*.**		4
2. 16:00	14:15	7.27	045	047	0.21	1	4
3. 23:59	23:59				*.**		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? N

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? N

   If Yes,

   a. Serial number:

Initials of person completing this form: KRF

SUPP05 Form Completion Date: 01/18/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 07 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? N

a. If Yes, Record the time of intubation

(hh:mm)

b. If Yes, Type of extubation:

1= Planned 2= Accidental

c. If Yes, Record the following prior to extubation

1. pH
2. PCO2
3. FiO2
4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Initials of person completing this form: KRP

SUPP05 Form Completion Date: 10/18/2005

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 08 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	04:00	7.31	046	061	0.21	1	4
2. 16:00	16:00	7.28	049	065	0.30	1	4
3. 23:59	23:59				0.28		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

   a. If Yes, Record the time of intubation

   b. Record the following prior to intubation: (hh:mm)

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other

         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRP**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 09 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.31		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **10** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**08:00**				**0.25**		**4**
2. 16:00	**16:00**				**0.26**		**4**
3. 23:59	**23:59**				**0.25**		**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **11** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**10:50**	**7.33**	**052**	***	**0.37**	**3**	**4**
2. 16:00	**16:00**				**0.27**		**4**
3. 23:59	**23:59**				**0.29**		**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **01/18/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 12 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.30		4
2. 16:00	16:00				0.34		4
3. 23:59	23:59				0.29		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 13 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	11:29	7.35	054	***	0.29	3	4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.31		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **01/18/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **14** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**03:54**	**7.35**	**052**	**056**	**0.31**	**1**	**4**
2. 16:00	**18:30**	**7.34**	**054**	***	**0.30**	**3**	**2**
3. 23:59	**23:59**				**0.21**		**2**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day?	**Y**
a. If Yes, Record the time of intubation	**18:00**
b. Record the following prior to intubation:	(hh:mm)
1. pH	**7.35**
2. PCO2	**052**
3. FiO2	**0.31**
4. Saturation	**090**
5. Apnea?	**Y**
6. Sepsis/R/O Sepsis?	**N**
7. Hemodynamic instability?	**N**
8. Clinically significant PDA?	**N**
9. Other	**N**
(specify)?	

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **01/18/2006**

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

SUPP10 Rel 2.0
March 10, 2005
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
02	(b) (6)	1	2	0	0	N	N	0	0	2	0	0	N	N	0	0		
03	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
04	(b) (6)	1	9	2	2	N	N	0	0	9	2	2	N	N	0	0		
05	(b) (6)	2	3	2	2	N	N	0	0	3	2	2	N	N	0	0		
06	(b) (6)	2	2	0	0	N	N	0	0	2	0	0	N	N	0	0	N	
07	(b) (6)	2	4	0	0	N	N	0	0	4	0	0	N	N	0	0		Y
08	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
09	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

RESPIRATORY SUPPORT AFTER 14 DAYS

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this form daily from study 15 through 36 weeks or status, whichever comes first.

Day of Life	Date	Higest Level of Support	Oxygen	Flow Rate	Form Creation Date	Form Creation Date
015	(b) (6)	2	Y		20051018	20051018
016		2	Y		20051018	20051018
017		2	Y		20051018	20051018
018		2	Y		20051018	20051018
019		2	Y		20051018	20051018
020		2	Y		20051018	20051018
021		4	Y		20051018	20051018
022		4	N		20051018	20051018
023		4	Y		20051018	20051018
024		4	Y		20051018	20051018
025		4	Y		20051018	20051018
026		4	Y		20051018	20051018
027		4	Y		20060118	20060118
028		4	Y		20060118	20060118
029		4	Y		20060118	20060118
030		4	Y		20060118	20060118
031		4	Y		20060118	20060118
032		4	Y		20060118	20060118
033		2	Y		20060118	20060118
034		2	Y		20060118	20060118
035		2	Y		20060118	20060118
036		2	Y		20060118	20060118
037		4	Y		20060118	20060118
038		4	Y		20060118	20060118
039		4	Y		20060118	20060118
040		4	Y		20060118	20060118
041		4	Y		20060118	20060118
042		4	N		20060118	20060123
043		5	Y	02.000	20060118	20060118
044		5	Y	02.000	20060118	20060118
045		4	N		20060118	20060118
046		4	Y		20060118	20060118
047		4	Y		20060118	20060118
048		4	N		20060118	20060118
049		4	N		20060118	20060118
050		4	N		20060118	20060118
051		4	N		20060118	20060118
052		4	N		20060118	20060118
053		4	N		20060118	20060118
054		6	Y		20060118	20060118
055		4	N		20060118	20060118

1= HFV 2= CV 3= Nasal SIMV 4= CPAP *5= NC 6=Hood 7=No Support 8=Infant temporarily out of unit

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RESPIRATORY SUPPORT AFTER 14 DAYS

CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete this form daily from study 15 through 36 weeks or status, whichever comes first.

Day of Life	Date	Higest Level of Support	Oxygen	Flow Rate	Form Creation Date	Form Creation Date
056	(b) (6)	4	N		20060118	20060118
057		4	N		20060118	20060118
058		4	N		20060118	20060118
059		4	N		20060118	20060118
060		4	N		20060118	20060118
061		4	N		20060118	20060118
062		4	Y		20060118	20060118
063		5	Y	01.500	20060118	20060118
064		5	Y	01.500	20060118	20060118
065		5	Y	01.500	20060118	20060118
066		5	Y	01.500	20060118	20060118
067		5	Y	01.500	20060118	20060118
068		5	Y	01.500	20060118	20060118
069		5	Y	01.500	20060118	20060118
070		5	Y	01.500	20060118	20060118
071		5	Y	01.500	20060118	20060118
072		5	Y	01.500	20060118	20060118
073		5	Y	01.500	20060118	20060118
074		5	Y	01.500	20060118	20060118
075		5	Y	01.500	20060118	20060118
076		5	Y	01.500	20060118	20060118
077		5	Y	01.500	20060118	20060118
078		5	Y	01.500	20060118	20060118

1= HFV 2= CV 3= Nasal SIMV 4= CPAP *5= NC 6=Hood 7=No Support 8=Infant temporarily out of unit

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): **21**
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: **08**
   b. Parity: **03**
4. Marital Status: **1**

   1 = Married 2 = Single 6 = Unknown

5. Highest level of education achieved by the Biological Mother: **3**

   1 = < 7th grade
   2 = 7th to 9th grade
   3 = 10th to 12th grade
   4 = High School degree
   5 = Partial college
   6 = College degree
   7 = Graduate degree
   8 = Unknown

6. Mother's medical insurance: **1**

   1 = Medicaid
   2 = Medicaid HMO
   3 = Private
   4 = Other HMO
   5 = Self-pay
   6 = Unknown
   7 = Both private public (e.g. Medicaid; CHIPS) assistance
   8 = No insurance upon admission

B. PREGNANCY COMPLICATION

1. Multiple birth? **N**
   a. If YES, Number of fetuses:
2. Mother had at least one pre-natal care visit for this pregnancy? **Y**
3. Was this pregnancy the product of artificial reproductive technology? **N**
4. Diabetes - insulin dependent? **N**
5. Hypertension/pre-eclampsia/eclampsia? **Y**
6. Antepartum hemorrhage? **N**

C. LABOR AND DELIVERY

1. Rupture of membranes:
   a. Date: (b) (6) (Month Day Year) b. Time: **08:00** (Hour Min)
2. Was there labor? **N**

   If YES, onset of labor:

   a. Date: (Month Day Year) b. Time: (Hour Min)
3. Were steroids given prior to delivery to accelerate maturity? **Y**
   a. If YES, Type of antenatal steroid given: **1**

   1 = Betamethasone 2 = Dexamethasone 3 = Both

   b. Was a complete course given within 7 days prior to delivery? **Y**
   c. Total number of courses given during this pregnancy: **01**
4. Were tocolytics used during the admission resulting in this delivery? **Y**
5. Were antibiotics used during the admission resulting in this delivery? **Y**
6. Final mode of delivery: **3**

   1 = Vaginal vertex 2 = Vaginal breech 3 = Cesarean section

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: **14:07** (Hour Min)

2. Was the infant outborn? **N**

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year) b. Time: (Hour Min)

3. Did the infant die <= 12 hours? **N**

   IF YES, COMPLETE FORM NG03E

4. Sex: **1**

   1 = Male 2 = Female 3 = Ambiguous

5. Race: **1**

   1 = Black, not Hispanic
   2 = White, not Hispanic
   3 = Hispanic, White
   4 = Hispanic, Black
   5 = American Indian or Alaska Native
   6 = Asian or Pacific Islander
   7 = Other

6. Gestational age:

   a. Weeks: **24** b. Days: **2**

7. Apgar score - 1 minute: **01**
8. Apgar score - 5 minutes: **07**
9. Delivery room resuscitation:
   - a. Oxygen? **Y**
   - b. Bagging and mask? **Y**
   - c. Chest compression? **N**
   - d. Intubation? **Y**
   - e. Drugs? **N**
10. Birth Weight: (grams): **0700**
11. Length (cm): **30.0**
12. Head Circumference (cm): **22.0**
13. Was cord blood gas done? **N**

    If Yes,

    a. Cord arterial pH (if done):
    b. Cord venous pH (if done):
    c. Cord pH (unknown vessel):
    d. Arterial base deficit (if done):
    e. Venous base deficit (if done):
    f. Base deficit (unknown vessel):

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

14. Infant's temperature on initial admission to the nursery from L&D (C) **36.2**

a. Source: **2**

1 = Rectal 2 = Axillary 3 = Skin

b. Date: (b) (6) [redacted] (Month Day Year) c. Time: **14:30** (Hour Min)

Initials of person completing this form: **KRF**

Form Completion Date: **10/18/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 1

```
1 = Discharged to home                    4 = Transferred to chronic care facility
2 = Still in hospital at 120 days         5 = Death
3 = Transferred to another hospital
```

2. Date of status: (b) (6) (Month Day Year)
3. Weight at status (grams): 1995
4. Length at status (cm): 38.0
5. Head circumference at status (cm): 32.0
6. Was respiratory support withheld and/or withdrawn at any time between birth and 24 hours after the infant was born? N

B. PULMONARY

1. Respiratory distress:
   a. Required oxygen at 6 hours of life continuing to age 24 hours? Y
   b. Demonstrated clinical features of respiratory distress within age 24 hrs? Y
   c. Had need for respiratory support to age 24 hours? Y
   d. Had an abnormal chest x-ray within age 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, total number of surfactant doses: 002
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Chest x-ray done after 21 days of age? Y

   If YES,

   a. Was x-ray consistent with BPD? Y
   b. If YES, date of x-ray after day 21 and closest to day 28 used to meet criteria: (b) (6) (Month Day Year)
6. Did baby require supplemental O2 at 36 weeks? Y
7. Was chest x-ray done at 36 weeks? Y

   If Yes,

a. Was x-ray consistent with BPD/CLD? N
   b. Date of x-ray at 36 weeks: (b) (6) (Month Day Year)
8. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: (Month Day Year)
9. Conventional ventilator? Y
10. High frequency ventilator? N

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES,
   a. Indomethacin for PDA? Y
   b. Surgery for PDA? N

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any indication? N
   If YES,
   a. Date: [redacted] (Month Day Year) b. Time: [redacted] (Hour Min)
2. Seizures? N
   a. If YES, Confirmed by EEG? [redacted]
3. Were any cranial sonograms done within 28 days of birth? Y
   If NO, Go to Question D6
   a. If Yes, Were all studies Normal? Y
   If Yes, Go to Question D6
   b. Date of sonogram for most severe hemorrhage: [redacted]
   Month Day Year
   c. Blood/echodensity in germinal matrix/subependymal area? [redacted]
   d. Blood/echodensity in the ventricle? [redacted]
   e. Blood/echodensity in the parenchyma? [redacted]
   f. Ventricular size enlarged? [redacted]
4. Cystic area(s) in the parenchyma within 28 days? [redacted]
5. Periventricular leukomalacia within 28 days? [redacted]
6. Were any cranial sonograms done after 28 days of birth? Y

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

7. Cranial sonogram closest to 36 weeks postconceptional age:
   a. Date of sonogram: (b) (6) Month Day Year
   b. Normal study? Y
      If YES, Go to Question 8
   c. Ventricular size enlarged?
   d. Cystic area(s) in the parenchyma?
   e. Cystic periventricular leukomalacia?
   f. Porencephalic cyst?
8. Surgical placement of a shunt for post hemorrhagic hydrocephalus/ persistent ventriculomegaly? N

E. INFECTION

1. Intra-uterine infection? N
   If YES, organism code(s): a. b.
2. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
3. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
4. Number of episodes of late onset culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 02
5. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y

   If YES,

   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 02
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	(b) (6)	104		
2	(b) (6)	230		
3				
4				
5				
6				

6. Infection of meninges/brain? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

F. GASTROINTESTINAL

1. Did the infant lose weight? Y
   a. If YES, Lowest weight? 0500
      1) Date of lowest weight: (b) (6) Month Day Year
   b. If YES, Did the infant regain birth weight? Y
      1) If YES, Date when first regained: **/**/**** Month Day Year
2. Did the baby receive patenteral alimentation? Y
   If YES,
   a. Date of first patenteral alimentation (b) (6) Month Day Year
   b. Parenteral alimentation, total number of days: 049
3. Did the baby receive enteral feeds? Y
   If YES,
   a. Date of first enteral feed: (b) (6) Month Day Year
   b. Were full enteral feeds achieved? Y
      1) If YES, date first achieved: (b) (6) Month Day Year
4. Proven NEC: 0

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode? Month Day Year
5. Spontaneous gastrointestinal perforation? N
   a. If YES, date of the first spontaneous gastrointestinal perforation: Month Day Year
6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **2**

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

         Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   a. If YES, was ROP diagnosed? **Y**

      1) If ROP diagnosed, record highest stage in lowest zone:

         i. Highest Stage:

	a) Right (OD)	b) Left (OS)
	2	**2**

         0 = No disease 2 = Stage II 4 = Stage IV
         1 = Stage I 3 = Stage III 5 = Stage V

         ii. Lowest Zone:

	a) Right (OD)	b) Left (OS)
	2	**2**

         1 = Zone I 2 = Zone II 3 = Zone III

         iii. Plus Disease?

	a) Right (OD)	b) Left (OS)
	N	**N**

      2) If ROP diagnosed, was threshold ROP diagnosed at any time?

         i. Right **Y**

         ii. Left **Y**

      3). Intervention Therapies:

         a. Was retinal ablation performed prior to a threshold diagnosis?

            i. Right: **N**

            ii. Left **N**

         b. Was any surgery performed? (Enter Code)

            i. Right: **0**

            ii. Left: **0**

            0 = None 1 = Lasertherapy 2 = Cryotherapy
            3 = Scleral buckle 4 = Other (specify)

            If Other(4) for Right eye, Specify

            If Other(4) for Left eye, Specify

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CENTER: 19 NETWORK(b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

4) If ROP diagnosed, were the ROP findings regressing at time of status?

a. Right: Y

b. Left: Y

I. SYNDROMES

1. Syndromes and/or major malformations? N

a. If YES, code:

1) 2) 3)

4) 5)

b) If a syndrome is coded 999, specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? Y

a. If YES, code:

1) **212** 2) 3)

4) 5)

i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

K. 28 DAY ANTHROPOMETRICS

1. Status at 28 Days: 2

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date at 28 Days: (b) (6)
Month Day Year

b. Weight (g): 0632

c. Length (cm): 36.0

d. Head circumference (cm): 22.0

L. 36 WEEK INFORMATION

1. Status at 36 weeks: 2

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks: (b) (6)
Month Day Year

b. Weight (g) 1361

c. Length (cm): 38.0

d. Head circumference (cm) 29.3

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is 3 or 4

1. Date of transfer:
Month Day Year

2. Transferred on oxygen?

3. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = In hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q.A1) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is "Discharged to home."

1. Date of discharge to home: (b) (6)
Month Day Year

2. Discharged home on oxygen? N

3. Discharged home on any of the following medications? Y

If YES,

a. Diuretics? Y

b. Bronchodilators? N

c. Anticonvulsants? N

d. Antireflux medications? Y

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

O. DEATH

1. Date of Death: Month Day Year

2. Time of death: Hour Min

3. Autopsy requested?

   a. If YES, Was consent granted?

4. Autopsy performed?

5. Cause of death

```
Malformation
10 = Congenital malformation
Pulmonary
20 = RDS
21 = RDS with severe intracranial hemorrhage
hemorrhage
22 = RDS with infection
25 = BPD
26 = BPD with infection
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

```
NEC
  40 = NEC
  41 = NEC with sepsis
CNS Insult
  50 = Severe intracranial

Other
  60 = Immaturity
  90 = Other
  99 = Unknown
```

6. If cause of death is code 10 (Congenital malformation), or code 90 (other), specify:

7. Was respiratory support withheld or withdrawn at any time after first 24hrs and prior to death?

Initials of person completing this form: LPK

Form Completion Date: 10/18/2005

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

CUMULATIVE DATA

	AT 24 HOURS	DAY 3	DAY 7	DAY 14	DAY 21	DAY 28	36 WEE	STATUS
1. NUMBER OF DAYS ON HFV:	N	0	0	00	00	00	00	000
2. NUMBER OF DAYS ON CV:	Y	3	4	05	11	11	14	014
3. NUMBER OF DAYS ON NASAL SIMV:	N	0	0	00	00	00	00	000
4. NUMBER OF DAYS ON CPAP:	N	0	3	09	10	17	45	045
5. NUMBER DAYS ON SUPPLEMENTAL O2:	N	2	6	13	20	27	63	064
6. NUMBER OF DAYS ON OXYGEN VIA HOOD/ISOLETTE:	N	0	0	00	00	00	01	001
7. NUMBER OF DAYS ON OXYGEN BY NASAL CANNULA:	N	0	0	00	00	00	23	034
8. HIGHEST FIO2:	0.21	0.21	0.21	0.31	0.41	0.40	0.25	0.25
OR								
9. SUPPLEMENTAL O2 BY NASAL CANNULA?								
10. IF IN ROOM AIR, BY NASAL CANNULA OR CPAP?	N	N	N					

Form Completion Date: 09/18/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **23:53**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **2**

   1= Blue 2= Orange

Initials of person completing this form: **KJA**

SUPP02 Form Completion Date: **11/15/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: (b) (6) (Month Day Year) b. Time: 23:53 (Hour Min)

2. Was CPAP initiated in the DR? Y

   If Yes, Date and time of CPAP initiation:

   a. Date: (b) (6) (Month Day Year) b. Time: 23:53 (Hour Min)

   c. Device: 1

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? N

   If Yes,

   a. Maximum PEEP:

5. Was intubation attempted in the DR? N

   If Yes, was the intubation successful?

6. Indication for intubation:

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR?

   b. Poor color?

   c. Apnea?

   d. Other?

   If Other specify:

   If (3) Other, specify:

7. Did the infant receive surfactant in the DR?

   If Yes, Date and time of administration:

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Type:

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: KJA

SUPP03 Form Completion Date: 03/13/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 00:15 (Hour Min)

2. Respiratory Support on admission to the NICU: 4

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: ***

4. FiO2: 0.80

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 00:52 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.30

   e. pCO2: 050

   f. pO2: 054

   g. FiO2: 0.22

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 23:54 (Hour Min)

   c. Serial number: 316783

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? N

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1			
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KJA

SUPP04 Form Completion Date: 08/08/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 01 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**:**						
2. 16:00	**:**						
3. 23:59	23:59				0.24		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **02** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**08:30**	**7.42**	**035**	**073**	**0.21**	**1**	**4**
2. 16:00	**16:00**				**0.21**		**4**
3. 23:59	**23:59**				**0.21**		**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KJA**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 03 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KJA**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 04 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 05 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 06 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation (hh:mm)
   b. Record the following prior to intubation:
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 07 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	05:35	7.26	041	038	0.21	3	4
2. 16:00	16:00				0.29		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 08 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	12:00	7.24	043	025	0.21	3	4
2. 16:00	16:00				0.25		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 2

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 09 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	05:25	7.23	044	026	0.21	3	4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.25		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 2

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 10 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.21		4
3. 23:59	23:59				0.21		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 2

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **11** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**03:59**	**7.34**	**040**	**071**	**0.21**	**1**	**4**
2. 16:00	**16:00**				**0.21**		**4**
3. 23:59	**23:59**				**0.21**		**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **2**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KRF**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: 12 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	08:00				0.21		4
2. 16:00	16:00				0.26		4
3. 23:59	23:59				0.24		4

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used 6

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? N
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **13** 2. Date: (b) (6) [redacted]

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**05:03**	**7.31**	**052**	**036**	**0.23**	**3**	**4**
2. 16:00	**16:00**				**0.27**		**4**
3. 23:59	**23:59**				**0.24**		**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**

a. If Yes, Record the time of intubation

b. Record the following prior to intubation: (hh:mm)

1. pH
2. PCO2
3. FiO2
4. Saturation
5. Apnea?
6. Sepsis/R/O Sepsis?
7. Hemodynamic instability?
8. Clinically significant PDA?
9. Other

(specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **08/08/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: **14** 2. Date: (b) (6)

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode** of Support
1. 08:00	**08:00**				**0.21**		**4**
2. 16:00	**16:00**				**0.31**		**4**
3. 23:59	**22:15**	**7.27**	**063**	**030**	**0.32**	**3**	**4**

* 1 = Arterial 2 = Venous 3 = Capillary

** 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

4. If Mode of Support is CPAP, type used **6**

2=Ventilator 5=Bubble 6=Flow Driver 9=Other

If (9) Other specify type:

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

B. SUPPLEMENTAL OXYGEN INFORMATION:

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO2	d. Flow Rate	e.** Mode of O2 Delivery
1. 12:00 (Noon)				

** 5 = Cannula 6 = Hood

C. INTUBATED/EXTUBATED INFORMATION: (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? **N**
   a. If Yes, Record the time of intubation
   b. Record the following prior to intubation: (hh:mm)
      1. pH
      2. PCO2
      3. FiO2
      4. Saturation
      5. Apnea?
      6. Sepsis/R/O Sepsis?
      7. Hemodynamic instability?
      8. Clinically significant PDA?
      9. Other
         (specify)?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

2. Was the Infant extubated on this day? **N**

   a. If Yes, Record the time of intubation

   (hh:mm)

   b. If Yes, Type of extubation:

   1= Planned 2= Accidental

   c. If Yes, Record the following prior to extubation

      1. pH
      2. PCO2
      3. FiO2
      4. Saturation

3. Was a replacement study oximeter placed on this infant on this day? **N**

   If Yes,

   a. Serial number:

Initials of person completing this form: **KLS**

SUPP05 Form Completion Date: **02/14/2007**

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

SUPP10 Rel 2.0
March 10, 2005
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
02	(b) (6)	1	2	2	2	N	N	0	0	2	1	1	N	N	0	0		
03	(b) (6)	1	2	2	2	N	N	0	0	2	1	1	N	N	0	0		
04	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
05	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
06	(b) (6)	1	2	3	3	N	N	0	0	2	3	3	N	N	0	0		
07	(b) (6)	2	2	3	3	N	Y	0	0	2	3	3	N	N	0	0		
08	(b) (6)	2	4	0	0	N	N	0	0	4	0	0	N	N	0	0	N	N
09	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
10	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
11	(b) (6)	2	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
12	(b) (6)	2	2	3	3	N	N	0	0	2	3	3	N	N	0	0		
13	(b) (6)	2	4	0	0	N	N	0	0	4	0	0	N	N	0	0	N	
14	(b) (6)	2	9	2	2	N	N	0	0	9	2	2	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
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9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

RESPIRATORY SUPPORT AFTER 14 DAYS

CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete this form daily from study 15 through 36 weeks or status, whichever comes first.

Day of Life	Date	Higest Level of Support	Oxygen	Flow Rate	Form Creation Date	Form Creation Date
015	(b) (6)	4	Y		20060313	20060808
016		4	Y		20060808	20060808
017		2	Y		20060808	20060808
018		2	Y		20060808	20060808
019		2	Y		20060313	20060313
020		2	Y		20060313	20060313
021		2	Y		20060313	20060313
022		2	Y		20060313	20060313
023		2	Y		20060313	20060313
024		2	Y		20060313	20060313
025		2	Y		20060313	20060313
026		2	Y		20060313	20060313
027		2	Y		20060313	20060313
028		2	Y		20060313	20060313
029		2	Y		20060313	20060313
030		2	Y		20060313	20060313
031		2	Y		20060313	20060313
032		2	Y		20060313	20060313
033		2	Y		20060313	20060313
034		2	Y		20060313	20060313
035		2	Y		20060313	20060313
036		2	Y		20060313	20060313
037		2	Y		20060313	20060313
038		2	Y		20060313	20060313
039		4	Y		20060313	20060313
040		4	Y		20060313	20060313
041		4	Y		20060313	20060313
042		4	Y		20060313	20060313
043		4	Y		20060313	20060313
044		4	Y		20060313	20060313
045		4	Y		20060313	20060313
046		4	Y		20060313	20060313
047		4	Y		20060313	20060313
048		4	Y		20060313	20060313
049		4	Y		20060313	20060313
050		4	Y		20060313	20060313
051		4	Y		20060313	20060313
052		4	Y		20060313	20060313
053		4	Y		20060313	20060313
054		4	Y		20060313	20060313
055		4	Y		20060313	20060313

1= HFV 2= CV 3= Nasal SIMV 4= CPAP *5= NC 6=Hood 7=No Support 8=Infant temporarily out of unit

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RESPIRATORY SUPPORT AFTER 14 DAYS

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this form daily from study 15 through 36 weeks or status, whichever comes first.

Day of Life	Date	Higest Level of Support	Oxygen	Flow Rate	Form Creation Date	Form Creation Date
056	(b) (6) [redacted]	4	Y		20060313	20060313
057		4	Y		20060313	20060313
058		5	Y	02.000	20060313	20060313
059		5	Y	02.000	20060313	20060313
060		5	Y	02.000	20060313	20060313
061		5	Y	02.000	20060313	20060313
062		5	Y	02.000	20060313	20060313
063		5	Y	02.000	20060313	20060313
064		5	N	02.000	20060313	20060313
065		5	Y	02.000	20060313	20060313
066		5	Y	02.000	20060313	20060313
067		5	N	02.000	20060313	20060313
068		5	N	02.000	20060313	20060313
069		5	N	01.500	20060313	20090813

1= HFV 2= CV 3= Nasal SIMV 4= CPAP *5= NC 6=Hood 7=No Support 8=Infant temporarily out of unit

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 28
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 01
   b. Parity: 01
4. Marital Status: 2

   1 = Married 2 = Single 6 = Unknown
5. Highest level of education achieved by the Biological Mother: 8

   1 = < 7th grade
   2 = 7th to 9th grade
   3 = 10th to 12th grade
   4 = High School degree
   5 = Partial college
   6 = College degree
   7 = Graduate degree
   8 = Unknown
6. Mother's medical insurance: 6

   1 = Medicaid
   2 = Medicaid HMO
   3 = Private
   4 = Other HMO
   5 = Self-pay
   6 = Unknown
   7 = Both private public (e.g. Medicaid; CHIPS) assistance
   8 = No insurance upon admission

B. PREGNANCY COMPLICATION

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother had at least one pre-natal care visit for this pregnancy? Y
3. Was this pregnancy the product of artificial reproductive technology? N
4. Diabetes - insulin dependent? N
5. Hypertension/pre-eclampsia/eclampsia? Y
6. Antepartum hemorrhage? N

C. LABOR AND DELIVERY

1. Rupture of membranes:
   a. Date: (b) (6) Month Day Year b. Time: **:** Hour Min
2. Was there labor? N

   If YES, onset of labor:

   a. Date: Month Day Year b. Time: Hour Min
3. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

   1 = Betamethasone 2 = Dexamethasone 3 = Both
   b. Was a complete course given within 7 days prior to delivery? Y
   c. Total number of courses given during this pregnancy: 01
4. Were tocolytics used during the admission resulting in this delivery? Y
5. Were antibiotics used during the admission resulting in this delivery? Y
6. Final mode of delivery: 1

   1 = Vaginal vertex 2 = Vaginal breech 3 = Cesarean section

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: 23:53 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year) b. Time: (Hour Min)

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 2

   1 = Male 2 = Female 3 = Ambiguous

5. Race: 1

   1 = Black, not Hispanic
   2 = White, not Hispanic
   3 = Hispanic, White
   4 = Hispanic, Black
   5 = American Indian or Alaska Native
   6 = Asian or Pacific Islander
   7 = Other

6. Gestational age:

   a. Weeks: 24 b. Days: 0

7. Apgar score - 1 minute: 02

8. Apgar score - 5 minutes: 06

9. Delivery room resuscitation:

   a. Oxygen? Y

   b. Bagging and mask? N

   c. Chest compression? N

   d. Intubation? N

   e. Drugs? N

10. Birth Weight: (grams): 0650

11. Length (cm): 31.0

12. Head Circumference (cm): 21.0

13. Was cord blood gas done? N

    If Yes,

    a. Cord arterial pH (if done):

    b. Cord venous pH (if done):

    c. Cord pH (unknown vessel):

    d. Arterial base deficit (if done):

    e. Venous base deficit (if done):

    f. Base deficit (unknown vessel):

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

14. Infant's temperature on initial admission to the nursery from L&D (C) **36.5**

a. Source: **2**

1 = Rectal 2 = Axillary 3 = Skin

b. Date: (b) (6) [redacted] (Month Day Year) c. Time: **00:15** (Hour Min)

Initials of person completing this form: **KLS**

Form Completion Date: **10/25/2005**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 3

```
1 = Discharged to home                    4 = Transferred to chronic care facility
2 = Still in hospital at 120 days         5 = Death
3 = Transferred to another hospital
```

2. Date of status: (b) (6)
   Month Day Year
3. Weight at status (grams): 1355
4. Length at status (cm): 39.4
5. Head circumference at status (cm): 26.5
6. Was respiratory support withheld and/or withdrawn at any time between birth and 24 hours after the infant was born? N

B. PULMONARY

1. Respiratory distress:
   a. Required oxygen at 6 hours of life continuing to age 24 hours? Y
   b. Demonstrated clinical features of respiratory distress within age 24 hrs? Y
   c. Had need for respiratory support to age 24 hours? Y
   d. Had an abnormal chest x-ray within age 24 hours? Y
2. Did the baby receive surfactants? N
   a. If YES, total number of surfactant doses:
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Chest x-ray done after 21 days of age? Y

   If YES,

   a. Was x-ray consistent with BPD? Y
   b. If YES, date of x-ray after day 21 and closest to day 28 used to meet criteria: (b) (6)
      Month Day Year
6. Did baby require supplemental O2 at 36 weeks? N
7. Was chest x-ray done at 36 weeks? N

   If Yes,

   a. Was x-ray consistent with BPD/CLD?
   b. Date of x-ray at 36 weeks:
      Month Day Year
8. Steroids for BPD/CLD? N
   a. If YES, Date of first dose:
      Month Day Year
9. Conventional ventilator? Y
10. High frequency ventilator? N

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

C. CARDIAC

1. Patent ductus arteriosus (PDA)? N

If YES,

a. Indomethacin for PDA?

b. Surgery for PDA?

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any indication? Y

If YES,

a. Date: (b) (6) (Month Day Year) b. Time: 03:00 (Hour Min)

2. Seizures? N

a. If YES, Confirmed by EEG?

3. Were any cranial sonograms done within 28 days of birth? Y

If NO, Go to Question D6

a. If Yes, Were all studies Normal? Y

If Yes, Go to Question D6

b. Date of sonogram for most severe hemorrhage:

Month Day Year

c. Blood/echodensity in germinal matrix/subependymal area?

d. Blood/echodensity in the ventricle?

e. Blood/echodensity in the parenchyma?

f. Ventricular size enlarged?

4. Cystic area(s) in the parenchyma within 28 days?

5. Periventricular leukomalacia within 28 days?

6. Were any cranial sonograms done after 28 days of birth? Y

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

7. Cranial sonogram closest to 36 weeks postconceptional age:
   a. Date of sonogram: (b) (6) Month Day Year
   b. Normal study? Y
      If YES, Go to Question 8
   c. Ventricular size enlarged?
   d. Cystic area(s) in the parenchyma?
   e. Cystic periventricular leukomalacia?
   f. Porencephalic cyst?
8. Surgical placement of a shunt for post hemorrhagic hydrocephalus/ persistent ventriculomegaly? N

E. INFECTION

1. Intra-uterine infection? N
   If YES, organism code(s): a. b.
2. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
3. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
4. Number of episodes of late onset culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 03
5. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 04
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	(b) (6)	104		
2	(b) (6)	811		
3	(b) (6)	104		
4	(b) (6)	811		
5				
6				

6. Infection of meninges/brain? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

F. GASTROINTESTINAL

1. Did the infant lose weight? Y
   a. If YES, Lowest weight? 0571
      1) Date of lowest weight: (b) (6) Month Day Year
   b. If YES, Did the infant regain birth weight? Y
      1) If YES, Date when first regained: (b) (6) Month Day Year
2. Did the baby receive patenteral alimentation? Y
   If YES,
   a. Date of first patenteral alimentation (b) (6) Month Day Year
   b. Parenteral alimentation, total number of days: 032
3. Did the baby receive enteral feeds? Y
   If YES,
   a. Date of first enteral feed: (b) (6) Month Day Year
   b. Were full enteral feeds achieved? Y
      1) If YES, date first achieved: (b) (6) Month Day Year
4. Proven NEC: 0

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode? Month Day Year
5. Spontaneous gastrointestinal perforation? N
   a. If YES, date of the first spontaneous gastrointestinal perforation: Month Day Year
6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **3**

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   a. If YES, was ROP diagnosed? **Y**

      1) If ROP diagnosed, record highest stage in lowest zone:

         i. Highest Stage:

a) Right (OD)	b) Left (OS)
3	**3**

         0 = No disease 2 = Stage II 4 = Stage IV
         1 = Stage I 3 = Stage III 5 = Stage V

         ii. Lowest Zone:

a) Right (OD)	b) Left (OS)
2	**2**

         1 = Zone I 2 = Zone II 3 = Zone III

         iii. Plus Disease?

a) Right (OD)	b) Left (OS)
N	**N**

      2) If ROP diagnosed, was threshold ROP diagnosed at any time?

         i. Right **N**

         ii. Left **N**

      3). Intervention Therapies:

         a. Was retinal ablation performed prior to a threshold diagnosis?

            i. Right: **N**

            ii. Left **N**

         b. Was any surgery performed? (Enter Code)

            i. Right: **0**

            ii. Left: **0**

            0 = None 1 = Lasertherapy 2 = Cryotherapy
            3 = Scleral buckle 4 = Other (specify)

            If Other(4) for Right eye, Specify

            If Other(4) for Left eye, Specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

4) If ROP diagnosed, were the ROP findings regressing at time of status?

a. Right: Y

b. Left: Y

I. SYNDROMES

1. Syndromes and/or major malformations? N

a. If YES, code:

1) 2) 3)

4) 5)

b) If a syndrome is coded 999, specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

a. If YES, code:

1) 2) 3)

4) 5)

i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

K. 28 DAY ANTHROPOMETRICS

1. Status at 28 Days: 2

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date at 28 Days: (b) (6) Month Day Year

b. Weight (g): 0748

c. Length (cm): ***.*

d. Head circumference (cm): **.*

L. 36 WEEK INFORMATION

1. Status at 36 weeks: 3

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks: Month Day Year

b. Weight (g)

c. Length (cm):

d. Head circumference (cm)

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is 3 or 4

1. Date of transfer: (b) (6) Month Day Year

2. Transferred on oxygen? N

3. Final outcome: 2

1 = Died in Hospital 2 = Discharged to Home 6 = In hospital at one year

a. If discharged to home, final weight at discharge (grams): 1972

N. DISCHARGE ALIVE

Complete this section if status (Q.A1) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is "Discharged to home."

1. Date of discharge to home: (b) (6) Month Day Year

2. Discharged home on oxygen? N

3. Discharged home on any of the following medications? Y

If YES,

a. Diuretics? Y

b. Bronchodilators? N

c. Anticonvulsants? N

d. Antireflux medications? N

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

O. DEATH

1. Date of Death: [redacted] Month Day Year

2. Time of death: [redacted] Hour Min

3. Autopsy requested? [redacted]

   a. If YES, Was consent granted? [redacted]

4. Autopsy performed? [redacted]

5. Cause of death [redacted]

```
Malformation
10 = Congenital malformation
Pulmonary
20 = RDS
21 = RDS with severe intracranial hemorrhage
hemorrhage
22 = RDS with infection
25 = BPD
26 = BPD with infection
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection

NEC
  40 = NEC
  41 = NEC with sepsis
CNS Insult
  50 = Severe intracranial

Other
  60 = Immaturity
  90 = Other
  99 = Unknown
```

6. If cause of death is code 10 (Congenital malformation), or code 90 (other), specify: [redacted]

7. Was respiratory support withheld or withdrawn at any time after first 24hrs and prior to death? [redacted]

Initials of person completing this form: [redacted]

Form Completion Date: 09/19/2009

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NICU Network

GENERIC DATABASE
RESPIRATORY SUPPORT FORM

NG07 V02 Rel 1.0
February 14, 2002

CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

	CUMULATIVE DATA							
	AT 24 HOURS	DAY 3	DAY 7	DAY 14	DAY 21	DAY 28	36 WEE	STATUS
1. NUMBER OF DAYS ON HFV:	N	0	0	00	00	00		000
2. NUMBER OF DAYS ON CV:	N	0	0	00	03	10		019
3. NUMBER OF DAYS ON NASAL SIMV:	N	0	0	00	00	00		000
4. NUMBER OF DAYS ON CPAP:	Y	3	7	14	17	17		037
5. NUMBER DAYS ON SUPPLEMENTAL O2:	Y	1	2	09	16	23		062
6. NUMBER OF DAYS ON OXYGEN VIA HOOD/ISOLETTE:	N	0	0	00	00	00		000
7. NUMBER OF DAYS ON OXYGEN BY NASAL CANNULA:	N	0	0	00	00	00		022
8. HIGHEST FIO2:	0.21	0.21	0.29	0.32	0.32	0.48		0.21
OR								
9. SUPPLEMENTAL O2 BY NASAL CANNULA?								
10. IF IN ROOM AIR, BY NASAL CANNULA OR CPAP?	N	Y						N

Form Completion Date: 09/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **11:30**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **2**

   1= Blue 2= Orange

Initials of person completing this form: **KJA**

SUPP02 Form Completion Date: **08/28/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: (b) (6) (Month Day Year) b. Time: 11:50 (Hour Min)

2. Was CPAP initiated in the DR? Y

   If Yes, Date and time of CPAP initiation:

   a. Date: (b) (6) (Month Day Year) b. Time: 12:03 (Hour Min)

   c. Device: 1

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

   If Yes,

   a. Maximum PEEP: 05

5. Was intubation attempted in the DR? Y

   If Yes, was the intubation successful? Y

6. Indication for intubation: 2

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR? Y

   b. Poor color? Y

   c. Apnea? Y

   d. Other? N

   If Other specify:

   If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

   If Yes, Date and time of administration:

   a. Date: (b) (6) (Month Day Year) b. Time: 12:15 (Hour Min)

   c. Type: 1

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

```
1 = Admitted to NICU for further care
2 = Infant Died
```

Initials of person completing this form: KRF

SUPP03 Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 12:30 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 094

4. FiO2: 0.21

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 18:10 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.19

   e. pCO2: 072

   f. pO2: 036

   g. FiO2: 0.29

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

   c. Serial number: 316382

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	20:55	1
2	(b) (6)	16:01	1
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KRF

SUPP04 Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	**:**								
2. 04:00	**:**								
3. 06:00	**:**								
4. 08:00	**:**								
5. 10:00	**:**								
6. 12:00	**:**				*.**		*		
7. 14:00	14:00				0.28		2		
8. 16:00	16:00	*.**	***	***	0.28	*	2		
9. 18:00	18:10				0.29		2		
10. 20:00	20:44				0.26		2		
11. 22:00	22:00				0.25		2		
12. 23:59	23:59	*.**	***	***	0.24	*	2		

13. Oximeter Alam Check (record every 6 hours)

a. 12:30 hr : min b. 20:00 hr : min c. 23:59 hr : min d. **:** hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.24		2	[redacted]	[redacted]
2. 04:00	04:00				0.21		2	[redacted]	[redacted]
3. 06:00	06:00				0.21		2	[redacted]	[redacted]
4. 08:00	08:00	*.**	***	***	0.21	*	2	[redacted]	[redacted]
5. 10:00	10:00				0.21		2	[redacted]	[redacted]
6. 12:00	12:00				0.21		2	[redacted]	[redacted]
7. 14:00	14:00				0.21		2	[redacted]	[redacted]
8. 16:00	16:00	*.**	***	***	0.21	*	2	[redacted]	[redacted]
9. 18:00	18:00				0.21		2	[redacted]	[redacted]
10. 20:00	20:00				0.21		2	[redacted]	[redacted]
11. 22:00	22:00				0.21		2	[redacted]	[redacted]
12. 23:59	23:59	7.33	034	039	0.21	1	2	[redacted]	[redacted]

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number: [redacted]

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		2		
2. 04:00	04:00				0.21		2		
3. 06:00	06:00				0.21		2		
4. 08:00	08:00	*.**	***	***	0.21	*	2		
5. 10:00	10:00				0.21		2		
6. 12:00	12:00				0.21		2		
7. 14:00	14:00				0.21		2		
8. 16:00	16:26	7.29	045	047	0.21	*	2		
9. 18:00	18:00				0.24		2		
10. 20:00	20:00				0.23		2		
11. 22:00	22:00				0.23		2		
12. 23:59	23:59	*.**	***	***	0.23	*	2		

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.23		2		
2. 04:00	04:40				0.21		2		
3. 06:00	06:00				0.21		2		
4. 08:00	08:00	*.**	***	***	0.21	*	2		
5. 10:00	10:00				0.23		2		
6. 12:00	12:58				0.23		2		
7. 14:00	14:00				0.23		2		
8. 16:00	16:00	*.**	***	***	0.22	*	2		
9. 18:00	18:30				0.23		2		
10. 20:00	20:00				0.25		2		
11. 22:00	22:00				0.24		2		
12. 23:59	23:59	*.**	***	***	0.24	*	2		

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.26		2		
2. 04:00	04:00				0.26		2		
3. 06:00	06:00				0.26		4		6
4. 08:00	09:00	7.24	051	045	0.24	1	4		6
5. 10:00	10:00				0.23		4		6
6. 12:00	12:00				0.25		4		6
7. 14:00	14:00				0.22		4		6
8. 16:00	16:00	*.**	***	***	0.23	*	4		6
9. 18:00	18:00				0.22		4		6
10. 20:00	20:00				0.22		4		6
11. 22:00	22:00				0.23		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/19/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4	[redacted]	6
2. 04:00	04:00				0.21		4	[redacted]	6
3. 06:00	06:00				0.21		4	[redacted]	6
4. 08:00	08:00	*.**	***	***	0.21	*	4	[redacted]	6
5. 10:00	10:00				0.21		4	[redacted]	6
6. 12:00	12:00				0.21		4	[redacted]	6
7. 14:00	14:00				0.21		4	[redacted]	6
8. 16:00	16:00	*.**	***	***	0.21	*	4	[redacted]	6
9. 18:00	18:00				0.21		4	[redacted]	6
10. 20:00	20:00				0.21		4	[redacted]	6
11. 22:00	22:00				0.21		4	[redacted]	6
12. 23:59	23:59	*.**	***	***	0.21	*	4	[redacted]	6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 09/22/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: XRF

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.23		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.23		4		6
6. 12:00	12:00				0.24		4		6
7. 14:00	14:00				0.30		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.23		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				*.**		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: XRF

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:35 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 09/22/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.23	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRP

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.23	*	4		6
5. 10:00	10:00				0.26		4		6
6. 12:00	12:00				0.22		4		6
7. 14:00	14:00				0.26		4		6
8. 16:00	16:00	*.**	***	***	0.26	*	4		6
9. 18:00	18:00				0.26		4		6
10. 20:00	20:00				0.23		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.26		4		6
6. 12:00	12:00				0.26		4		6
7. 14:00	14:00				0.26		4		6
8. 16:00	16:00	*.**	***	***	0.26	*	4		6
9. 18:00	18:00				0.24		4		6
10. 20:00	20:00				0.24		4		6
11. 22:00	22:00				0.26		4		6
12. 23:59	23:59	*.**	***	***	0.32	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 16:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 09/22/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: ARF

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

SUPP10 Rel 2.0
March 10, 2005
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	2	1	1	N	N	0	0	2	0	0	N	N	0	0		
02	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
03	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
04	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
05	**/**/2006	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
06	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
07	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
08	(b) (6)	1	3	1	1	N	N	0	0	3	1	1	N	N	0	0		
09	(b) (6)	2	3	1	1	N	N	0	0	3	1	1	N	N	0	0	Y	Y

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	015
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	016
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	017
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	018
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	019
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	020
Date	[redacted] (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	021
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	022
Date	[redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** Birth No: 1

Study Day	023
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	024
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	025
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/22/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	026
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	027
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	028
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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Study Day	029
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	030
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	031
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	033
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	034
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	035
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	036
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:58

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	037
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	038
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	039
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	040
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/24/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	041
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	042
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	043
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	044
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	045
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	046
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	047
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	048
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	049
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/24/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	050
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 01/23/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	051
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	052
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	053
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	054
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	22:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	055
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	056
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	057
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	058
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	059
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	060
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	061
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	062
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/24/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	063
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/24/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	064
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	065
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/24/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	066
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	067
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	068
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/24/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	069
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/24/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	070
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	071
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	072
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	073
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	074
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	075
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	076
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	19:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	077
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	078
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 05/06/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	079
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/18/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 34
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 04
   b. Parity: 02
4. Marital Status: 2

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 4

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 1

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? N
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? U
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? N

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3. Were maternal antibiotics used during the admission resulting in this delivery? Y

   a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

   1. 01 3. 5.

   2. 4. 6.

4. Final mode of delivery: 1

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: 11:50 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 2

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 1

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 24 b. Days: 6

8. Apgar score - 1 minute: 03

9. Apgar score - 5 minutes: 08

10. Birth resuscitation/stabilization:

    a. Oxygen? Y

    b. Bagging and mask? N

    c. CPAP? Y

    d. Intubation? Y

    e. Chest compression? N

    f. Epinephrine? N

11. Birth Weight: (grams): 0530

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

12. Length (cm): 29.5
13. Head Circumference (cm): 21.5
14. Was cord blood gas done? Y

    If Yes,

    a. Cord pH (any vessel): 7.41
    b. Base deficit (any vessel): [redacted]

15. Was Infant's first temperature within 60 minutes of birth? Y

    If Yes,

    1. Centigrade: 36.9 2. Fahrenheit: [redacted]

    a. Date: (b) (6) (Month Day Year) b. Time: 12:30 (Hour Min)

    c. Source: 2

1 = Rectal	2 = Axillary	3 = Skin

Initials of person completing this form: KRF

Form Completion Date: 01/17/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 2

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6)
Month Day Year

3. Weight at status (grams): 2590
4. Length at status (cm): 49.0
5. Head circumference at status (cm): 34.5

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) 12:15
   Month Day Year Hours Min
   b. Total number of surfactant doses: 003
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose:
   Month Day Year
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES, treatment:
   a. Indomethacin? Y
   If YES, total number of courses 01
   b. Ibuprofin N
   If YES, total number of courses
   c. Surgery? Y

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? Y
   If YES,
   a. Date: (b) (6) b. Time: 20:00
   Month Day Year Hour Min
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 2

   b. Date of image: (b) (6) [redacted]
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 03
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 01
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	(b) (6)	104		
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0462
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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2. Did the baby receive patenteral alimentation? **Y**

   If YES,

   a. Date of first patenteral alimentation (b) (6)

   b. Total number of days: **058**

3. Did the baby receive enteral feeds? **Y**

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? **Y**

      1) If YES, date first achieved: (b) (6)

   c. Did the baby receive breast milk in the first 28 days? **Y**

      1) If YES, number of days baby received any breast milk in first 28 days: **15**

4. Proven NEC: **0**

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

      Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? **N**

   a. If YES, date of the first spontaneous gastrointestinal perforation:

      Month Day Year

6. Did the infant have GI surgery that resulted in short gut? **N**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **2**

1 = OAE	2 = AABR	3 = ABR	4 = OAE + AABR	5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

Results:	1. Pass	2. Fail	3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

Results:	1. Pass	2. Fail	3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **N**

      2) Did plus disease develop in either eye? **N**

      3) Other therapies

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **N**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **1**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? **N**

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? **Y**

   a. If YES, code:

1) =	**206**	2) =	**999**	3) =
4) =		5) =		

   i) If a major surgery is coded 999, specify:

   nissen funduplication

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K. 36 WEEK INFORMATION

1. Status at 36 weeks: **2**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) **1262**

c. Length (cm): **34.0**

d. Head circumference (cm) **27.5**

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home:
Month Day Year

2. Discharged home on continuous oxygen?

3. Discharged home on any of the following medications?

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage
22 = RDS with infection                         Other
25 = BPD                                          60 = Immaturity
26 = BPD with infection                           90 = Other
27 = BPD with severe CNS insult                   99 = Unknown
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: **KRF**

Form Completion Date: **01/22/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	00	00	03	003
2. On CV?	Y	Y	2. Number of days on CV	3	5	05	17	30	033
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	00	000
4. On CPAP	N	N	4. Number days on CPAP	0	2	09	11	38	044
			5. Number of days on supplemental O2	3	5	08	22	55	055
6. FiO2	0.21	0.21	6. Highest FIO2 on day	0.24	0.23	0.32	0.34		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	Y	N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?						N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation [redacted]

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field [redacted]

d. If on nasal cannula at time of challenge, record flow rate [redacted]

e. Did the patient pass the evaluation? [redacted]

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason: [redacted]

If 9, explain [redacted]

```
1= Increased FIO2                                  4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)    6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)          9= Other-explain
```

Form Completion Date: **09/19/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6) Month Day Year

   b. Time: **10:45** Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **1**

   1= Blue 2= Orange

Initials of person completing this form: **KRF**

SUPP02 Form Completion Date: **11/16/2006**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

a. Date: (b) (6) (Month Day Year) b. Time: 10:45 (Hour Min)

2. Was CPAP initiated in the DR? Y

If Yes, Date and time of CPAP initiation:

a. Date: (b) (6) (Month Day Year) b. Time: 10:45 (Hour Min)

c. Device: 1

1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

If Yes,

a. Maximum PEEP: 05

5. Was intubation attempted in the DR? N

If Yes, was the intubation successful?

6. Indication for intubation:

1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

If (2) Resuscitation,

a. Low HR?

b. Poor color?

c. Apnea?

d. Other?

If Other specify:

If (3) Other, specify:

7. Did the infant receive surfactant in the DR?

If Yes, Date and time of administration:

a. Date: (Month Day Year) b. Time: (Hour Min)

c. Type:

1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: KRF

SUPP03 Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 11:03 (Hour Min)

2. Respiratory Support on admission to the NICU: 4

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 096

4. FiO2: 0.28

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 12:10 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.24

   e. pCO2: 059

   f. pO2: 066

   g. FiO2: 0.24

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 10:55 (Hour Min)

   c. Serial number: 316779

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? Y

   If Yes,

   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

   c. Indication for intubation:

      1. Surfactant? N
      2. FiO2 > .50 to maintain SaO2 >= 88% N
      3. pCO2 > 65 on single blood gas? N
      4. Apnea requiring bag and mask ventilation? N
      5. If NO to all above, state reason: 3

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

         frequent apnea and bradycardia

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation? N

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? N

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1			
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KLS

SUPP04 Form Completion Date: 02/27/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO_2	(e) PO_2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	**:**								
2. 04:00	**:**								
3. 06:00	**:**								
4. 08:00	**:**								
5. 10:00	**:**								
6. 12:00	12:10				0.24		4		6
7. 14:00	14:48				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:00	7.39	039	048	0.21	1	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 11:00 hr : min b. 20:00 hr : min c. hr : min d. hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:05	7.42	027	060	0.21	1	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.21	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.21		4		6
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.23	*	4		6
9. 18:00	18:00				0.22		4		6
10. 20:00	20:00				0.22		4		6
11. 22:00	22:00				0.24		4		6
12. 23:59	23:59	*.**	***	***	0.24	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 09:00 hr : min b. 12:00 hr : min c. 17:00 hr : min d. 23:00 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.24		4		6
2. 04:00	04:00				0.23		4		6
3. 06:00	06:00				0.23		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		4		6
6. 12:00	12:00				0.21		4		6
7. 14:00	14:00				0.21		4		6
8. 16:00	16:00	*.**	***	***	0.23	*	4		6
9. 18:00	18:00				0.21		4		6
10. 20:00	20:00				0.23		4		6
11. 22:00	22:00				0.23		4		6
12. 23:59	23:59	*.**	***	***	0.23	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 05:00 hr : min b. 11:00 hr : min c. 16:00 hr : min d. 23:00 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4	[redacted]	6
2. 04:00	04:00				0.23		4	[redacted]	6
3. 06:00	06:00				0.23		4	[redacted]	6
4. 08:00	08:00	*.**	***	***	0.23	*	4	[redacted]	6
5. 10:00	10:00				0.22		4	[redacted]	6
6. 12:00	12:00				0.23		4	[redacted]	6
7. 14:00	14:00				0.23		4	[redacted]	6
8. 16:00	16:00	*.**	***	***	0.23	*	4	[redacted]	6
9. 18:00	18:00				0.24		4	[redacted]	6
10. 20:00	20:00				0.21		4	[redacted]	6
11. 22:00	22:00				0.21		4	[redacted]	6
12. 23:59	23:59	*.**	***	***	0.21	*	4	[redacted]	6

13. Oximeter Alam Check (record every 6 hours)

a. 05:00 hr : min b. 11:00 hr : min c. 17:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	4		6
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 18:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 11/16/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 11/16/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 16:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 11/16/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRE

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		2		
2. 04:00	04:00				0.23		2		
3. 06:00	06:00				0.21		2		
4. 08:00	09:10	7.30	045	042	0.21	3	2		
5. 10:00	10:00				0.21		2		
6. 12:00	12:00				0.21		2		
7. 14:00	14:00				0.21		2		
8. 16:00	16:00	*.**	***	***	0.21	*	2		
9. 18:00	18:00				0.21		2		
10. 20:00	20:00				0.21		2		
11. 22:00	22:00				0.21		4		6
12. 23:59	23:59	*.**	***	***	0.21	*	4		6

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 11/16/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		4		6
2. 04:00	04:00				0.21		4		6
3. 06:00	06:00				0.21		4		6
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 04:00 hr : min b. 08:00 hr : min c. 12:00 hr : min d. 20:00 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 08:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

Form Completion Date: 11/16/2006

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 06:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRP

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

A. Record blood gas results, FiO2 and Respiratory Support closest to the Scheduled Time. If no blood gases were measured, enter FiO2 and Respiratory Support.

a. Scheduled Time	(b) Time Measured (hour:min)	(c) pH	(d) CO2	(e) PO2	(f) FiO2	(g)* Source	(h).** Mode of Support	(i) If Mode=5 record flow rate	***(j) If Mode=4 (CPAP) Type used
1. 02:00	02:00				0.21		7		
2. 04:00	04:00				0.21		7		
3. 06:00	06:00				0.21		7		
4. 08:00	08:00	*.**	***	***	0.21	*	7		
5. 10:00	10:00				0.21		7		
6. 12:00	12:00				0.21		7		
7. 14:00	14:00				0.21		7		
8. 16:00	16:00	*.**	***	***	0.21	*	7		
9. 18:00	18:00				0.21		7		
10. 20:00	20:00				0.21		7		
11. 22:00	22:00				0.21		7		
12. 23:59	23:59	*.**	***	***	0.21	*	7		

13. Oximeter Alam Check (record every 6 hours)

a. 04:00 hr : min b. 12:00 hr : min c. 20:00 hr : min d. 23:59 hr : min

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

14. Was a replacement study oximeter placed on this infant on this day? N

If Yes,

a. Serial number:

15. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 11/16/2006

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: . Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	3	0	0	N	N	0	0	2	0	0	N	N	0	0	Y	
02	(b) (6)	1	4	0	0	N	N	0	0	4	0	0	N	N	0	0	Y	Y

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	015
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	016
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	017
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	018
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	10:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	19:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	019
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	020
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 12/01/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	021
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 12/01/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	022
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	023
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	024
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

Study Day	025
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	026
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	027
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 11/16/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	028
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	11:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	**:**
18:00	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	**:**
23:59	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 02/27/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 27
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 02
   b. Parity: 01
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 8

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 9

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? Y
7. Was a placental pathology performed? N
   If YES,
   a. Was histologic chorioamnionitis documented?

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? Y
   If Yes,
   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)
   c. If date and/or time unknown, were ROM estimated at > 18 hours? Y
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? U

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3. Were maternal antibiotics used during the admission resulting in this delivery? Y

   a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

   1. 01 3. 49 5.

   2. 32 4. 6.

4. Final mode of delivery: 1

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: 10:45 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date:

   Month Day Year

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 2

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 1

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 27 b. Days: 3

8. Apgar score - 1 minute: 09

9. Apgar score - 5 minutes: 09

10. Birth resuscitation/stabilization:

    a. Oxygen? Y

    b. Bagging and mask? N

    c. CPAP? Y

    d. Intubation? N

    e. Chest compression? N

    f. Epinephrine? N

11. Birth Weight: (grams): 1035

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

12. Length (cm): 35.5

13. Head Circumference (cm): 24.0

14. Was cord blood gas done? N

If Yes,

a. Cord pH (any vessel):

b. Base deficit (any vessel):

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: **.*

2. Fahrenheit:

a. Date: (b) (6) (Month Day Year)

b. Time: **:** (Hour Min)

c. Source: 2

1 = Rectal	2 = Axillary	3 = Skin

Initials of person completing this form: KRP

Form Completion Date: 12/01/2006

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 3

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) Month Day Year
3. Weight at status (grams): 1071
4. Length at status (cm): **.*
5. Head circumference at status (cm): **.*

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? N
   a. If YES, date and time of first dose: Month Day Year Hours Min
   b. Total number of surfactant doses:
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: Month Day Year
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? N
   If YES, treatment:
   a. Indomethacin?
   If YES, total number of courses
   b. Ibuprofin
   If YES, total number of courses
   c. Surgery?

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? N
   If YES,
   a. Date: Month Day Year b. Time: Hour Min
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 2

   b. Date of image: (b) (6) Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 00
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 01
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	(b) (6)	699		
2				
3				
4				
5				
6				

5. Meningitis? Y
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	(b) (6)	104		
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0851
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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2. Did the baby receive patenteral alimentation? Y

   If YES,

   a. Date of first patenteral alimentation (b) (6)

   b. Total number of days: 014

3. Did the baby receive enteral feeds? Y

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? Y

      1) If YES, date first achieved: (b) (6)

   c. Did the baby receive breast milk in the first 28 days? Y

      1) If YES, number of days baby received any breast milk in first 28 days: 24

4. Proven NEC: 0

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

      Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? N

   a. If YES, date of the first spontaneous gastrointestinal perforation:

      Month Day Year

6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? N

a. If YES, hearing screen protocol used:

1 = OAE	2 = AABR	3 = ABR	4 = OAE + AABR	5 = Other

b. Final screen results before discharge

i) Right ear:

ii) Left ear:

Results:	1. Pass	2. Fail	3. Incomplete

c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

1) If YES, answer the following:

i) Right ear:

ii) Left ear:

Results:	1. Pass	2. Fail	3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? N

If Yes,

a. Was ROP diagnosed in either eye?

If Yes,

1) Did it reach stage 3 or worse in either eye?

2) Did plus disease develop in either eye?

3) Other therapies

(if yes, specify):

b. Intervention Therapies:

1. Was retinal ablation performed in either eye (laser and/or cryotherapy)?

2. Was any scleral buckle or vitrectomy performed in either eye?

2. At the time of reaching status, indicate the most appropriate:

1 = Determined, favorable in both eyes

2 = Determined, severe ROP in either eye

3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM (b)(6) Mother's Initials: *** , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: 3

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: Month Day Year

b. Weight (g)

c. Length (cm):

d. Head circumference (cm)

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer: (b) (6) Month Day Year

2. Final outcome: 2

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams): 2115

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home: (b) (6) Month Day Year

2. Discharged home on continuous oxygen? Y

3. Discharged home on any of the following medications? Y

If YES,

a. Diuretics? Y

b. Bronchodilators? N

c. Anticonvulsants? N

d. Antireflux medications? N

O. DEATH

1. Date of Death: Month Day Year

a. Time of Death Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage                                      Other
22 = RDS with infection                           60 = Immaturity
25 = BPD                                          90 = Other
26 = BPD with infection                           99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: KLS

Form Completion Date: 09/17/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N		1. Number days on HFV	0	0	00	00		000
2. On CV?	N		2. Number of days on CV	0	0	01	01		001
3. On nasal SIMV?	N		3. Number of days on nasal SIMV	0	0	00	00		000
4. On CPAP	Y		4. Number days on CPAP	3	6	07	07		007
			5. Number of days on supplemental O2	2	4	05	10		010
6. FiO2	0.21		6. Highest FIO2 on day	0.24	0.21	0.21	0.21		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	Y		8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?		N	Y	N		N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation? [redacted]

IF YES to question C.1

a. Was the evaluation performed? [redacted]

b. Date of evaluation [redacted]

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field [redacted]

d. If on nasal cannula at time of challenge, record flow rate [redacted]

e. Did the patient pass the evaluation? [redacted]

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason: [redacted]

If 9, explain [redacted]

```
1= Increased FI02                                4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)  6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)        9= Other-explain
```

Form Completion Date: 09/18/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **06:32**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **2**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **2**

   1= Blue 2= Orange

Initials of person completing this form: **KRF**

SUPP02 Form Completion Date: **07/28/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

a. Date: (b) (6) (Month Day Year) b. Time: 06:32 (Hour Min)

2. Was CPAP initiated in the DR? N

If Yes, Date and time of CPAP initiation:

a. Date: (Month Day Year) b. Time: (Hour Min)

c. Device:

1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? *

If Yes,

a. Maximum PEEP:

5. Was intubation attempted in the DR? Y

If Yes, was the intubation successful? Y

6. Indication for intubation: 4

1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

If (2) Resuscitation,

a. Low HR?

b. Poor color?

c. Apnea?

d. Other?

If Other specify:

If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

If Yes, Date and time of administration:

a. Date: (b) (6) (Month Day Year) b. Time: 07:00 (Hour Min)

c. Type: 1

1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: (b)(6) Mother's Initials: , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: KRF

SUPP03 Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 07:00 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 096

4. FiO2: 0.21

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 07:55 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.34

   e. pCO2: 047

   f. pO2: 074

   g. FiO2: 0.21

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 07:00 (Hour Min)

   c. Serial number: 316783

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year

b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? N

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1			
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KJA

SUPP04 Form Completion Date: 08/01/2007

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Ver 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**				
2. 04:00	**:**				
3. 06:00	**:**				
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:58	7.34	047	074	0.21	1	2		
2. 16:00	16:00	7.36	040	056	0.21	1	2		
3. 24:00	01:44	7.37	040	119	0.21	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 10:00 b. 12:00 c. 18:00 d. 23:59

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KJA

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 14:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00									
2. 16:00									
3. 24:00									

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 12:00 c. 16:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	5	*.***	
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 12:00 c. 16:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 20:00 c. 23:59 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 12:00 c. 16:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRP

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	7		
2. 04:00	04:00	0.21	7		
3. 06:00	06:00	0.21	7		
4. 08:00	08:00	0.21	7		
5. 10:00	10:00	0.21	7		
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	7		
12. 24:00	23:59	0.21	7		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	23:50	7.25	042	035	0.21	3	7		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** [redacted]

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	7		
2. 04:00	04:00	0.21	7		
3. 06:00	06:00	0.21	7		
4. 08:00	08:00	0.27	7		
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	10:00	7.21	038	***	0.21	3	4		6
2. 16:00	14:45	7.25	039	***	0.21	3	4		6
3. 24:00	23:50	7.31	035	***	0.21	3	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. 20:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	04:13	7.28	038	***	0.21	3	4		6
2. 16:00	12:00	7.28	038	***	0.21	3	4		6
3. 24:00	22:25	7.29	042	***	0.21	3	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 10:00 c. 20:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:00	7.29	041	***	0.21	3	4		6
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	21:14	7.32	044	***	0.21	3	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 16:00 d. 21:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	04:43	7.33	044	***	0.21	3	4		6
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 05:00 b. 12:00 c. 16:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	7		
6. 12:00	12:00	0.21	7		
7. 14:00	14:00	0.21	7		
8. 16:00	16:00	0.21	7		
9. 18:00	18:00	0.21	7		
10. 20:00	20:00	0.21	7		
11. 22:00	22:00	0.21	7		
12. 24:00	23:59	0.21	7		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 09:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 09:00 b. 13:00 c. 17:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KRF

Form Completion Date: 08/01/2007

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	9	2	2	N	N	0	0	9	2	2	N	N	0	0		
02	(b) (6)	1	3	0	0	N	N	0	0	2	1	1	N	N	0	0		
03	(b) (6)	2	4	0	0	N	N	0	0	2	4	0	N	N	0	0		
04	(b) (6)	2	4	0	0	N	N	0	0	2	4	0	N	N	0	0		
05	(b) (6)																Y	N

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT: 0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	015
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	016
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	017
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	018
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	019
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	020
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	021
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	022
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	023
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	024
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	025
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	026
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 027

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 028

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 029

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 030

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	031
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	9
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
2. Scheduled Time:	
12:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
3. Scheduled Time:	
18:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
4. Scheduled Time:	
23:59	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 032

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 033

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 034

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 035

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	036
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	9
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
2. Scheduled Time:	
12:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
3. Scheduled Time:	
18:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
4. Scheduled Time:	
23:59	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 037

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
   06:00 (time measured)
   (a) Highest Level of Support (Mode) 9
   (b) Oxygen
   (c) Flow Rate (NC Only)
   (d) Oximeter Alarm Check

2. Scheduled Time:
   12:00 (time measured)
   (a) Highest Level of Support (Mode)
   (b) Oxygen
   (c) Flow Rate (NC Only)
   (d) Oximeter Alarm Check

3. Scheduled Time:
   18:00 (time measured)
   (a) Highest Level of Support (Mode)
   (b) Oxygen
   (c) Flow Rate (NC Only)
   (d) Oximeter Alarm Check

4. Scheduled Time:
   23:59 (time measured)
   (a) Highest Level of Support (Mode)
   (b) Oxygen
   (c) Flow Rate (NC Only)
   (d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 038

Date [redacted]
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 039

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 040

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day **041**

Date (b) (6)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **08/14/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day **042**

Date (b) (6)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **08/14/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 043

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day 044

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 045

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 046

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day **047**

Date (b) (6)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **08/14/2007**

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 048

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day: 049

Date: (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode): 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 050

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 051

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 052

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 053

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day **054**

Date (b) (6) [redacted]
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **08/14/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: , Birth No: 1

Study Day 055

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	056
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	9
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
2. Scheduled Time:	
12:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
3. Scheduled Time:	
18:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
4. Scheduled Time:	
23:59	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 057

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 058

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 059

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day 060

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day 061

Date [redacted] (b) [redacted]
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day 062

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)
(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day **063**

Date (b) (6)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **08/14/2007**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day **064**

Date [redacted](b)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day 065

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/14/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 18
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 01
   b. Parity: 01
4. Marital Status: 2

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 3

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 6

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? Y
6. Was Chorioamnionitis documented in the mother's medical record? N
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? N

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? Y

   a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

   1. 49 3. 5.

   2. 4. 6.

4. Final mode of delivery: 3

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: 06:32 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 2

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 1

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 27 b. Days: 5

8. Apgar score - 1 minute: 04

9. Apgar score - 5 minutes: 07

10. Birth resuscitation/stabilization:

   a. Oxygen? Y

   b. Bagging and mask? N

   c. CPAP? N

   d. Intubation? Y

   e. Chest compression? N

   f. Epinephrine? N

11. Birth Weight: (grams): 0885

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Birth weight (grams):

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

12. Length (cm): 36.0
13. Head Circumference (cm): 24.0
14. Was cord blood gas done? Y

If Yes,

a. Cord pH (any vessel): 7.32
b. Base deficit (any vessel): **

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: 36.6
2. Fahrenheit:

a. Date: (b) (6) (Month Day Year)
b. Time: 07:00 (Hour Min)

c. Source: 2

1 = Rectal 2 = Axillary 3 = Skin

Initials of person completing this form: KRF

Form Completion Date: 05/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: **1**

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) Month Day Year

3. Weight at status (grams): **1830**
4. Length at status (cm): **39.0**
5. Head circumference at status (cm): **29.5**

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? **Y**
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? **Y**
2. Did the baby receive surfactants? **Y**
   a. If YES, date and time of first dose: (b) (6) Month Day Year ****:**** Hours Min
   b. Total number of surfactant doses: **001**
3. Pneumothorax? **N**
4. Pulmonary hemorrhage? **N**
5. Steroids for BPD/CLD? **N**
   a. If YES, Date of first dose: Month Day Year
6. Did infant receive inhaled nitric oxide? **N**
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? **Y**
   If YES, treatment:
   a. Indomethacin? **N**
   If YES, total number of courses
   b. Ibuprofin **Y**
   If YES, total number of courses **01**
   c. Surgery? **N**

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? **N**
   If YES,
   a. Date: Month Day Year b. Time: Hour Min
2. Were there seizures treated with an anti-convulsant for >72 hours? **N**

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 2

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? N
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 01
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? N
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days:
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0781
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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2. Did the baby receive patenteral alimentation? **Y**

   If YES,

   a. Date of first patenteral alimentation **(b) (6)**

   b. Total number of days: **039**

3. Did the baby receive enteral feeds? **Y**

   If YES,

   a. Date of first enteral feed: **(b) (6)**

   b. Did enteral feeds reach 120 ml/kg/day? **Y**

      1) If YES, date first achieved: **(b) (6)**

   c. Did the baby receive breast milk in the first 28 days? **Y**

      1) If YES, number of days baby received any breast milk in first 28 days: **03**

4. Proven NEC: **0**

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

      Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? **N**

   a. If YES, date of the first spontaneous gastrointestinal perforation:

      Month Day Year

6. Did the infant have GI surgery that resulted in short gut? **N**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **2**

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **Y**

      2) Did plus disease develop in either eye? **N**

      3) Other therapies

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **N**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **3**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

```
1. Determined Favorable:
   -    Vessels mature (fully vascularized)
   -    Vessels in zone III for two consecutive exams
   -    ROP of stage 1 or 2 in zone III for two consecutive exams
   -    ROP in zone II or zone III but determined to be clearly regressing
```

```
2.  Determined-Severe:
    -    ROP surgery
    -    Retinal detachment
    -    Avastin injection
```

```
3.  Undetermined:
    -    Immature Vessels in zone I and II
    -    Immature Vessels reaching zone III for only 1 exam
    -    Stage 1 or 2 ROP in zone III for only 1 exam
    -    Stage 3 ROP in zone III
    -    ROP in zone I or zone II
    -    Plus disease
```

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: **2**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) **1732**

c. Length (cm): **39.0**

d. Head circumference (cm) **29.5**

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply **2**

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode: **2**

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home: (b)
Month Day Year

2. Discharged home on continuous oxygen? **N**

3. Discharged home on any of the following medications? **N**

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage                                      Other
22 = RDS with infection                           60 = Immaturity
25 = BPD                                          90 = Other
26 = BPD with infection                           99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: KJA

Form Completion Date: 11/01/2007

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CENTER: 19 NETWORK: (b) (6) SITENM (b) Mother's Initials: , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	00	00	00	000
2. On CV?	N	N	2. Number of days on CV	1	1	01	01	01	001
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	00	000
4. On CPAP	Y	N	4. Number days on CPAP	2	6	13	21	21	021
			5. Number of days on supplemental O2	1	1	01	01	01	001
6. FiO2	0.21	0.21	6. Highest FIO2 on day	0.21	0.21	0.21	0.21		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	Y	N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?	Y	Y	Y	N		N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FIO2                              4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)  6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)      9= Other-explain
```

Form Completion Date: 07/30/2007

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **18:31**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **1**

   1= Blue 2= Orange

Initials of person completing this form: **KRF**

SUPP02 Form Completion Date: **01/10/2008**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

a. Date: (b) (6) (Month Day Year) b. Time: 18:31 (Hour Min)

2. Was CPAP initiated in the DR? N

If Yes, Date and time of CPAP initiation:

a. Date: (Month Day Year) b. Time: (Hour Min)

c. Device:

1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

If Yes,

a. Maximum PEEP: 05

5. Was intubation attempted in the DR? Y

If Yes, was the intubation successful? Y

6. Indication for intubation: 2

1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

If (2) Resuscitation,

a. Low HR? Y

b. Poor color? Y

c. Apnea? Y

d. Other? N

If Other specify:

If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

If Yes, Date and time of administration:

a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

c. Type: 1

1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: SMC

SUPP03 Form Completion Date: 05/13/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 19:00 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 092

4. FiO2: 0.40

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 20:00 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.05

   e. pCO2: 078

   f. pO2: 083

   g. FiO2: 0.40

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 19:00 (Hour Min)

   c. Serial number: 316779

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	11:01	1
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: SMC

SUPP04 Form Completion Date: 01/10/2008

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Ver 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**				
2. 04:00	**:**				
3. 06:00	**:**				
4. 08:00	**:**				
5. 10:00	**:**				
6. 12:00	**:**				
7. 14:00	**:**				
8. 16:00	**:**				
9. 18:00	**:**				
10. 20:00	20:00	0.40	2		
11. 22:00	22:00	0.39	2		
12. 24:00	23:59	0.55	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	23:20	7.08	073	050	0.55	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 19:00 b. c. d.

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/10/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.60	1		
2. 04:00	04:00	0.30	1		
3. 06:00	06:00	0.30	1		
4. 08:00	08:00	0.30	1		
5. 10:00	10:00	0.29	1		
6. 12:00	12:00	0.30	1		
7. 14:00	14:00	0.60	1		
8. 16:00	16:00	0.38	1		
9. 18:00	18:00	0.40	1		
10. 20:00	20:00	0.30	1		
11. 22:00	22:00	0.30	1		
12. 24:00	23:59	0.30	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:25	7.19	045	045	0.30	1	1		
2. 16:00	16:15	7.02	081	050	0.38	1	1		
3. 24:00	22:20	7.28	049	041	0.30	1	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 16:00 b. 20:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.40	1		
2. 04:00	04:00	0.47	1		
3. 06:00	06:00	0.30	1		
4. 08:00	08:00	0.28	1		
5. 10:00	10:00	0.30	1		
6. 12:00	12:00	0.40	1		
7. 14:00	14:00	0.24	1		
8. 16:00	16:00	0.25	1		
9. 18:00	18:00	0.21	1		
10. 20:00	20:00	0.21	1		
11. 22:00	22:00	0.21	1		
12. 24:00	23:59	0.21	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:00	7.35	036	054	0.25	1	1		
2. 16:00	16:45	7.26	044	045	0.25	1	1		
3. 24:00	23:25	7.23	047	030	0.25	1	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 17:00 d. 20:00

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/10/2008

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.25	1		
2. 04:00	04:00	0.21	1		
3. 06:00	06:00	0.21	1		
4. 08:00	08:00	0.25	1		
5. 10:00	10:00	0.25	1		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	17:00	7.31	040	073	0.21	1	2		
3. 24:00	22:00	7.10	055	059	0.21	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 14:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.25	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.25	2		
9. 18:00	18:00	0.23	2		
10. 20:00	20:00	0.28	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:30	7.36	036	063	0.21	1	2		
2. 16:00	15:15	7.26	045	059	0.21	1	2		
3. 24:00	22:45	7.27	045	058	0.21	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 13:00 b. 20:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	*.**	*		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.25	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	08:10	7.27	050	068	0.21	1	2		
2. 16:00	17:30	7.24	051	047	0.28	1	2		
3. 24:00	00:10	7.29	046	063	0.21	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.25	2		
3. 06:00	06:00	0.25	2		
4. 08:00	08:00	0.28	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.30	2		
7. 14:00	14:00	0.30	2		
8. 16:00	16:00	0.29	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.23	2		
12. 24:00	23:59	0.23	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	08:35	7.32	044	072	0.28	1	2		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 09:00 b. 16:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	2		
2. 04:00	04:00	0.23	2		
3. 06:00	06:00	0.22	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.23	2		
7. 14:00	14:00	0.23	2		
8. 16:00	16:00	0.30	4		6
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.25	4		6
11. 22:00	22:00	0.25	4		6
12. 24:00	23:59	0.25	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:40	7.29	044	054	0.21	1	2		
2. 16:00	16:20	7.25	056	023	0.30	2	4		6
3. 24:00									

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.25	4		6
2. 04:00	04:00	0.32	4		6
3. 06:00	06:00	0.33	4		6
4. 08:00	08:00	0.25	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.22	4		6
11. 22:00	22:00	0.22	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.25	5	1.500	
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.22	4		6
6. 12:00	12:00	0.22	5	1.500	
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.23	4		6
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.31	4		6
11. 22:00	22:00	0.23	4		6
12. 24:00	23:59	0.23	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 20:00 c. 00:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	12:00	0.22	5	1.500	
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.23	4		6
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.31	4		6
11. 22:00	22:00	0.23	4		6
12. 24:00	23:59	0.23	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 00:00 b. 06:00 c. 12:00 d. 16:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/10/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.24	5	2.000	
2. 04:00	04:00	0.22	4		6
3. 06:00	06:00	0.22	4		6
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	12:00	0.28	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	5	1.500	
12. 24:00	23:59	0.21	5	1.500	

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 12:00 d. 16:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/10/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	10:00	7.32	036	042	0.21	1	4		6
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 00:00 b. 06:00 c. 20:00 d. 22:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 01/10/2008

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	1	2	2	N	N	0	0	1	2	2	N	N	0	0		
02	(b) (6)	1	1	2	2	N	N	0	0	1	2	2	N	N	0	0		
03	(b) (6)	1	1	2	2	N	N	0	0	1	2	2	N	N	0	0		
04	(b) (6)	1	1	2	2	N	N	0	0	2	3	3	N	N	0	0		
05	(b) (6)	1	1	2	2	N	N	0	0	2	3	3	N	N	0	0		
06	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
07	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
08	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
09	(b) (6)	1	2	3	3	N	N	0	0	2	3	3	N	N	0	0		
10	(b) (6)	1	2	3	3	N	Y	1	0	2	3	3	Y	Y	1	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT: 0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
11	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
12	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
13	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
14	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
15	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
16	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
17	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		N
18	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
19	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
20	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT: 0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM(b)(6) Mother's Initials: *** Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
21	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
22	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
23	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
24	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
25	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

*STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	015
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	016
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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Study Day	017
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	018
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	019
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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Study Day	020
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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Study Day	021
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	022
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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Study Day	023
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	024
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 07/01/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	025
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

Study Day	026
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	027
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** Birth No: 1

Study Day	028
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	029
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	030
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	031
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	032
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	033
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	22:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	034
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	035
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	036
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	22:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	037
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	038
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	039
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	040
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	041
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	042
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/14/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	043
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	044
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	045
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	046
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	047
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	048
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	6
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	049
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	050
Date	[redacted] (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	051
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	052
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/14/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	053
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	054
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	055
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	056
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	057
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	03:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	058
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	059
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	060
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	061
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	062
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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Study Day	063
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	14:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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Study Day	064
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

Study Day	065
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 066

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)
(a) Highest Level of Support (Mode) 5
(b) Oxygen N
(c) Flow Rate (NC Only) 02.000
(d) Oximeter Alarm Check 08:00

2. Scheduled Time: 12:00
12:00 (time measured)
(a) Highest Level of Support (Mode) 5
(b) Oxygen N
(c) Flow Rate (NC Only) 02.000
(d) Oximeter Alarm Check 12:00

3. Scheduled Time: 18:00
18:00 (time measured)
(a) Highest Level of Support (Mode) 5
(b) Oxygen N
(c) Flow Rate (NC Only) 01.500
(d) Oximeter Alarm Check **:**

4. Scheduled Time: 23:59
23:59 (time measured)
(a) Highest Level of Support (Mode) 5
(b) Oxygen N
(c) Flow Rate (NC Only) 01.500
(d) Oximeter Alarm Check **:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	067
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

Study Day	068
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	069
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	22:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	070
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	071
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	14:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	072
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	073
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	074
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	075
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/31/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	076
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	077
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	078
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	079
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	080
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day **081**

Date (b) (6)
Month Day Year

1. Scheduled Time: **06:00**

06:00 (time measured)

(a) Highest Level of Support (Mode) **9**

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **10/22/2008**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 082

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	083
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	9
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
2. Scheduled Time:	
12:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
3. Scheduled Time:	
18:00	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
4. Scheduled Time:	
23:59	(time measured)
(a) Highest Level of Support (Mode)	
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 10/22/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 32
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 02
   b. Parity: 02
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 8

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? Y
   a. If YES, Number of fetuses: 2
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? Y
6. Was Chorioamnionitis documented in the mother's medical record? N
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? N

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? Y

   a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

   1. 01 3. 5.

   2. 4. 6.

4. Final mode of delivery: 3

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: 18:31 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 1

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 7

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 24 b. Days: 2

8. Apgar score - 1 minute: 01

9. Apgar score - 5 minutes: 05

10. Birth resuscitation/stabilization:

    a. Oxygen? Y

    b. Bagging and mask? Y

    c. CPAP? N

    d. Intubation? Y

    e. Chest compression? N

    f. Epinephrine? N

11. Birth Weight: (grams): 0750

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CENTER: 19 NETWORK(b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

12. Length (cm): 33.0
13. Head Circumference (cm): 23.0
14. Was cord blood gas done? N

If Yes,

a. Cord pH (any vessel): [redacted]
b. Base deficit (any vessel): [redacted]

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: 36.3
2. Fahrenheit: [redacted]

a. Date: (b) (6) (Month Day Year)
b. Time: 19:00 (Hour Min)

c. Source: 2

1 = Rectal	2 = Axillary	3 = Skin

Initials of person completing this form: SMC

Form Completion Date: 01/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 2

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) (Month Day Year)
3. Weight at status (grams): 2065
4. Length at status (cm): 40.0
5. Head circumference at status (cm): 30.5

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) (Month Day Year) **:** (Hours Min)
   b. Total number of surfactant doses: 004
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: (Month Day Year)
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES, treatment:
   a. Indomethacin? N
   If YES, total number of courses
   b. Ibuprofin Y
   If YES, total number of courses 03
   c. Surgery? N

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? Y
   If YES,
   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? N

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: (b) (6)
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area? Y

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?	Y	Y
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?	Y	Y
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?	Y	Y
g. Blood/echo-density in the parenchyma?	N	N

4. Cystic area(s) in the parenchyma within 28 days? N

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 1

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? N

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?	N	N
e. Cystic periventricular leukomalacia?	N	N
f. Porencephalic cyst?	N	N

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? Y
   If YES, organism code(s): a. 200 b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 02
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? N
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days:
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0523
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

2. Did the baby receive patenteral alimentation? Y

   If YES,

   a. Date of first patenteral alimentation [redacted]

   b. Total number of days: 030

3. Did the baby receive enteral feeds? Y

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? Y

      1) If YES, date first achieved: (b) (6)

   c. Did the baby receive breast milk in the first 28 days? Y

      1) If YES, number of days baby received any breast milk in first 28 days: 02

4. Proven NEC: 0

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

   Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? N

   a. If YES, date of the first spontaneous gastrointestinal perforation:

   Month Day Year

6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? Y

   a. If YES, hearing screen protocol used: 2

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: 1

      ii) Left ear: 1

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? Y

   If Yes,

   a. Was ROP diagnosed in either eye? Y

      If Yes,

      1) Did it reach stage 3 or worse in either eye? Y

      2) Did plus disease develop in either eye? Y

      3) Other therapies

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? Y

      2. Was any scleral buckle or vitrectomy performed in either eye? N

2. At the time of reaching status, indicate the most appropriate: 3

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

```
1. Determined Favorable:
   -    Vessels mature (fully vascularized)
   -    Vessels in zone III for two consecutive exams
   -    ROP of stage 1 or 2 in zone III for two consecutive exams
   -    ROP in zone II or zone III but determined to be clearly regressing
```

```
2.  Determined-Severe:
    -    ROP surgery
    -    Retinal detachment
    -    Avastin injection
```

```
3.  Undetermined:
    -    Immature Vessels in zone I and II
    -    Immature Vessels reaching zone III for only 1 exam
    -    Stage 1 or 2 ROP in zone III for only 1 exam
    -    Stage 3 ROP in zone III
    -    ROP in zone I or zone II
    -    Plus disease
```

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   i) If a major surgery is coded 999, specify:

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K. 36 WEEK INFORMATION

1. Status at 36 weeks: **2**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) **1239**

c. Length (cm): **38.0**

d. Head circumference (cm) **28.7**

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home:
Month Day Year

2. Discharged home on continuous oxygen?

3. Discharged home on any of the following medications?

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

3. Contributory Cause of death

```
Malformation                                          NEC
10 = Congenital malformation                            40 = NEC
Pulmonary                                               41 = NEC with sepsis
20 = RDS                                              CNS Insult
21 = RDS with severe intracranial hemorrhage            50 = Severe intracranial
hemorrhage
22 = RDS with infection                               Other
25 = BPD                                                60 = Immaturity
26 = BPD with infection                                 90 = Other
27 = BPD with severe CNS insult                         99 = Unknown
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: MLD

Form Completion Date: 09/10/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b)(6) Mother's Initials: *** , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	Y	N	1. Number days on HFV	3	4	04	04	04	004
2. On CV?	N	N	2. Number of days on CV	0	3	04	11	12	012
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	00	000
4. On CPAP	N	N	4. Number days on CPAP	0	0	06	13	29	029
			5. Number of days on supplemental O2	3	7	13	27	70	070
6. FiO2	0.60	0.21	6. Highest FIO2 on day	0.47	0.30	0.21	0.25		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.		N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?			Y			N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FIO2                                  4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)    6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)          9= Other-explain
```

Form Completion Date: 08/31/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **11:30**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **2**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **1**

   1= Blue 2= Orange

Initials of person completing this form: **MLD**

SUPP02 Form Completion Date: **08/12/2008**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: (b) (6) (Month Day Year) b. Time: 11:52 (Hour Min)

2. Was CPAP initiated in the DR? N

   If Yes, Date and time of CPAP initiation:

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Device:

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

   If Yes,

   a. Maximum PEEP: 05

5. Was intubation attempted in the DR? Y

   If Yes, was the intubation successful? Y

6. Indication for intubation: 4

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR?

   b. Poor color?

   c. Apnea?

   d. Other?

   If Other specify:

   If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

   If Yes, Date and time of administration:

   a. Date: (b) (6) (Month Day Year) b. Time: 12:10 (Hour Min)

   c. Type: 1

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

8. Was active resuscitation required? **N**

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: **1**

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: **MLD**

SUPP03 Form Completion Date: **08/12/2008**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 12:25 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 094

4. FiO2: 0.60

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 12:55 (Hour Min)

   c. Source: 1

   1= Arterial 2= Venous 3= Capillary

   d. pH: 7.30

   e. pCO2: 055

   f. pO2: 120

   g. FiO2: 0.41

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 12:00 (Hour Min)

   c. Serial number: 315452

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

      1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

      If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? N

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1			
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: MLD

SUPP04 Form Completion Date: 04/28/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Ver 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006
Revised October 15, 2007

CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**				
2. 04:00	**:**				
3. 06:00	**:**				
4. 08:00	**:**				
5. 10:00	**:**				
6. 12:00	**:**	*.**	*		
7. 14:00	14:00	0.35	2		
8. 16:00	16:00	0.30	2		
9. 18:00	18:00	0.28	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	17:00	7.33	051	079	0.28	1	2		
3. 24:00	23:59	7.49	029	050	0.21	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 21:00 b. c. d.

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.35	4		6
10. 20:00	20:00	0.35	4		6
11. 22:00	22:00	0.32	4		6
12. 24:00	23:59	0.28	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	12:25	7.42	034	064	0.21	1	2		
3. 24:00	19:59	7.37	039	049	0.35	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.25	4		6
2. 04:00	04:00	0.25	4		6
3. 06:00	06:00	0.25	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 20:00 c. 23:59 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.25	5	1.500	
3. 06:00	06:00	0.25	5	1.500	
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	12:00	0.21	5	1.500	
7. 14:00	14:00	0.21	5	1.500	
8. 16:00	16:00	0.21	5	1.500	
9. 18:00	18:00	0.21	5	1.500	
10. 20:00	20:00	0.21	5	1.500	
11. 22:00	22:00	0.21	5	1.500	
12. 24:00	23:59	0.21	5	1.500	

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 12:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	5	1.500	
2. 04:00	04:00	0.21	5	1.500	
3. 06:00	06:00	0.21	5	1.500	
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	12:00	0.21	5	1.500	
7. 14:00	14:00	0.21	5	1.500	
8. 16:00	16:00	0.21	5	1.500	
9. 18:00	18:00	0.21	5	1.500	
10. 20:00	20:00	0.21	5	1.500	
11. 22:00	22:00	0.21	5	1.500	
12. 24:00	23:59	0.21	5	1.500	

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	5	1.500	
2. 04:00	04:00	0.21	5	1.500	
3. 06:00	06:00	0.21	5	1.500	
4. 08:00	08:00	0.21	5	1.500	
5. 10:00	10:00	0.21	5	1.500	
6. 12:00	10:00	0.21	7		
7. 14:00	14:00	0.21	7		
8. 16:00	16:00	0.21	7		
9. 18:00	18:00	0.21	7		
10. 20:00	20:00	0.21	7		
11. 22:00	22:00	0.21	7		
12. 24:00	23:59	0.21	7		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	7		
2. 04:00	04:00	0.21	7		
3. 06:00	06:00	0.21	7		
4. 08:00	08:00	0.21	7		
5. 10:00	10:00	0.21	7		
6. 12:00	12:00	0.21	7		
7. 14:00	14:00	0.21	7		
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 12:00 b. 20:00 c. 23:59 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/29/2008

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00									
2. 16:00									
3. 24:00									

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 20:00 b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	5	2.000	
11. 22:00	22:00	0.22	5	2.000	
12. 24:00	23:59	0.22	5	2.000	

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:51	7.09	055	034	0.21	3	4		6
2. 16:00	10:55	7.22	043	056	0.21	1	4		6
3. 24:00	20:20	7.20	046	030	0.21	3	5	2.000	

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 20:00 b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	5	2.000	
2. 04:00	04:00	0.21	5	2.000	
3. 06:00	06:00	0.22	5	2.000	
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.25	2		
9. 18:00	18:00	0.25	2		
10. 20:00	20:00	0.23	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	18:20	7.05	075	044	0.25	3	2		
3. 24:00	23:55	7.25	036	108	0.21	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 09:00 b. 16:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/29/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.25	2		
3. 06:00	06:00	0.25	2		
4. 08:00	08:00	0.28	2		
5. 10:00	10:00	0.30	2		
6. 12:00	12:00	0.27	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.25	2		
9. 18:00	18:00	0.25	2		
10. 20:00	20:00	0.23	2		
11. 22:00	22:00	0.23	2		
12. 24:00	23:59	0.25	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	10:20	7.11	073	048	0.30	3	2		
2. 16:00	17:45	7.18	062	041	0.25	3	2		
3. 24:00	21:15	7.21	062	042	0.23	3	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 03:00 b. 08:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.24	2		
2. 04:00	04:00	0.23	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.27	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	1		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.23	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	08:15	7.32	054	042	0.21	3	2		
2. 16:00	13:37	7.30	060	039	0.21	3	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. 16:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.25	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.25	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.23	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	03:14	7.32	060	034	0.21	3	2		
2. 16:00	16:55	7.36	058	032	0.21	3	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 16:00 c. 19:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.30	4		6
6. 12:00	12:00	0.30	4		6
7. 14:00	14:00	0.40	4		6
8. 16:00	16:00	0.30	4		6
9. 18:00	18:00	0.38	4		6
10. 20:00	20:00	0.40	4		6
11. 22:00	22:00	0.34	4		6
12. 24:00	23:59	0.31	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:30	7.36	056	041	0.21	3	2		
2. 16:00									
3. 24:00									

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 20:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 08/29/2008

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

SUPP10 Rel 2.0
March 10, 2005
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM(b)(6) Mother's Initials: , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	2	0	0	N	N	0	0	2	0	0	N	N	0	0		
02	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
03	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
04	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
05	(b) (6)	2	4	0	0	N	N	0	0	4	0	0	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	015
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	016
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	017
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	018
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	019
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	020
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	021
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	022
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	**.***
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	023
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	024
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	025
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	026
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	027
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	028
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Study Day	029
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	030
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	031
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	032
Date	[redacted] (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	033
Date	(b) (6) [redacted] 8 Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	034
Date	[redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	035
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	036
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	037
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	038
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	039
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	040
Date	[redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	041
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	042
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	043
Date	(b) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	044
Date	[redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	23:59
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	045
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	046
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	047
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	048
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: Birth No: 1

Study Day 049

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)
(a) Highest Level of Support (Mode) 5
(b) Oxygen N
(c) Flow Rate (NC Only) 02.000
(d) Oximeter Alarm Check 05:00

2. Scheduled Time: 12:00
12:00 (time measured)
(a) Highest Level of Support (Mode) 7
(b) Oxygen N
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check 13:00

3. Scheduled Time: 18:00
18:00 (time measured)
(a) Highest Level of Support (Mode) 7
(b) Oxygen N
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check **:**

4. Scheduled Time: 23:59
23:59 (time measured)
(a) Highest Level of Support (Mode) 7
(b) Oxygen N
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check **:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	050
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	051
Date	(b) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	21:00

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	052
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	N
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	053
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	10:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	054
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	18:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	055
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	N
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/12/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	056
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	08:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	**:**
23:59	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 08/13/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 26
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 02
   b. Parity: 01
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 6

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? Y
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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CENTER: 19 (b) (6) [redacted] SITENM (b) (6) Mother's Initials: *** , Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? Y

   a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

   1. 01 3. 61 5.
   2. 32 4. 6.

4. Final mode of delivery: 1

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) [redacted] (Month Day Year) b. Time: 11:52 (Hour Min)

2. Was the infant outborn? N

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

   IF YES, COMPLETE FORM NG03E

4. Sex: 1

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 2

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 25 b. Days: 5
8. Apgar score - 1 minute: 03
9. Apgar score - 5 minutes: 09
10. Birth resuscitation/stabilization:
    a. Oxygen? Y
    b. Bagging and mask? Y
    c. CPAP? N
    d. Intubation? Y
    e. Chest compression? N
    f. Epinephrine? N
11. Birth Weight: (grams): 0980

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CENTER: 19 (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

12. Length (cm): 40.0
13. Head Circumference (cm): 24.2
14. Was cord blood gas done? Y

If Yes,

a. Cord pH (any vessel): 7.42
b. Base deficit (any vessel): **

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: 37.1 2. Fahrenheit:

a. Date: (b) (6) (Month Day Year) b. Time: 12:30 (Hour Min)

c. Source: 2

1 = Rectal	2 = Axillary	3 = Skin

Initials of person completing this form: MLD

Form Completion Date: 06/13/2008

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 3

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) (Month Day Year)
3. Weight at status (grams): 1636
4. Length at status (cm): 43.0
5. Head circumference at status (cm): 29.5

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) (Month Day Year) 12:10 (Hours Min)
   b. Total number of surfactant doses: 001
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: (Month Day Year)
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES, treatment:
   a. Indomethacin? N
   If YES, total number of courses
   b. Ibuprofin N
   If YES, total number of courses
   c. Surgery? Y

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? N
   If YES,
   a. Date: (Month Day Year) b. Time: (Hour Min)
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings:
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 1

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 00
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? N
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days:
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0795
   b. Date of lowest weight in the first 10 days: [redacted]
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6) [redacted]

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2. Did the baby receive patenteral alimentation? Y

   If YES,

   a. Date of first patenteral alimentation (b) (6)

   b. Total number of days: 019

3. Did the baby receive enteral feeds? Y

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? Y

      1) If YES, date first achieved: (b) (6)

   c. Did the baby receive breast milk in the first 28 days? Y

      1) If YES, number of days baby received any breast milk in first 28 days: 21

4. Proven NEC: 0

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

      Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? N

   a. If YES, date of the first spontaneous gastrointestinal perforation:

      Month Day Year

6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **N**

   a. If YES, hearing screen protocol used:

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear:

      ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **N**

      2) Did plus disease develop in either eye? **N**

      3) Other therapies

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **N**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **3**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: (b) (6) (b) (6) Mother's Initials: *** , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? **N**

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? **N**

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: **3**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement:
Month Day Year

b. Weight (g)

c. Length (cm):

d. Head circumference (cm)

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer: (b) (6)
Month Day Year

2. Final outcome: **2**

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams): **2645**

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home: (b)
Month Day Year

2. Discharged home on continuous oxygen? **N**

3. Discharged home on any of the following medications? **N**

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM (b) Mother's Initials: *** , Birth No: 1

3. Contributory Cause of death

```
Malformation                                        NEC
10 = Congenital malformation                          40 = NEC
Pulmonary                                             41 = NEC with sepsis
20 = RDS                                            CNS Insult
21 = RDS with severe intracranial hemorrhage          50 = Severe intracranial
hemorrhage                                          Other
22 = RDS with infection                               60 = Immaturity
25 = BPD                                              90 = Other
26 = BPD with infection                               99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: MLD

Form Completion Date: 02/25/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) Mother's Initials: *** , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N		1. Number days on HFV	0	0	00	00		000
2. On CV?	Y		2. Number of days on CV	2	2	07	10		013
3. On nasal SIMV?	N		3. Number of days on nasal SIMV	0	2	02	02		014
4. On CPAP	N		4. Number days on CPAP	1	3	05	16		026
			5. Number of days on supplemental O2	3	7	14	28		054
6. FiO2	0.21		6. Highest FIO2 on day	0.23	0.21	0.40	0.26		0.23
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	Y		8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?		Y				

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FIO2                                4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)  6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)        9= Other-explain
```

Form Completion Date: 09/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **16:00**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **1**

   1= Blue 2= Orange

Initials of person completing this form: **MLD**

SUPP02 Form Completion Date: **03/03/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: (b) (6) (Month Day Year) b. Time: 16:32 (Hour Min)

2. Was CPAP initiated in the DR? Y

   If Yes, Date and time of CPAP initiation:

   a. Date: (b) (6) (Month Day Year) b. Time: 16:33 (Hour Min)

   c. Device: 1

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

   If Yes,

   a. Maximum PEEP: 05

5. Was intubation attempted in the DR? Y

   If Yes, was the intubation successful? Y

6. Indication for intubation: 2

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR? N

   b. Poor color? Y

   c. Apnea? Y

   d. Other? N

   If Other specify:

   If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

   If Yes, Date and time of administration:

   a. Date: (b) (6) (Month Day Year) b. Time: 16:45 (Hour Min)

   c. Type: 1

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

8. Was active resuscitation required? **N**

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: **1**

```
1 = Admitted to NICU for further care
2 = Infant Died
```

Initials of person completing this form: **MLD**

SUPP03 Form Completion Date: **03/03/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 17:05 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: 093

4. FiO2: 0.25

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 17:50 (Hour Min)

   c. Source: 1

   1= Arterial 2= Venous 3= Capillary

   d. pH: 7.29

   e. pCO2: 044

   f. pO2: 056

   g. FiO2: 0.30

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: 16:40 (Hour Min)

   c. Serial number: 316779

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

      1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

      If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year

b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	19:23	1
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: MLD

SUPP04 Form Completion Date: 03/03/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Ver 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006
Revised October 15, 2007

CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**				
2. 04:00	**:**				
3. 06:00	**:**				
4. 08:00	**:**				
5. 10:00	**:**				
6. 12:00	**:**				
7. 14:00	**:**				
8. 16:00	**:**				
9. 18:00	18:00	0.30	2		
10. 20:00	20:00	0.30	2		
11. 22:00	22:00	0.25	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	17:50	7.29	044	056	0.30	1	2		
3. 24:00	22:50	7.31	048	021	0.25	2	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 17:30 b. 20:00 c. 23:59 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.25	2		
5. 10:00	10:00	0.24	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.23	4		6
11. 22:00	22:00	0.23	4		6
12. 24:00	23:59	0.23	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	06:05	7.32	048	031	0.21	3	2		
2. 16:00	18:00	7.17	051	034	0.23	2	4		6
3. 24:00	23:54	7.31	047	023	0.23	2	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 03:07 b. 08:00 c. 20:00 d. 21:00

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	4		6
2. 04:00	04:00	0.23	4		6
3. 06:00	06:00	0.23	4		6
4. 08:00	08:00	0.27	4		6
5. 10:00	10:00	0.25	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.23	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.25	4		6
12. 24:00	23:59	0.25	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 19:23 c. 21:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.24	4		6
2. 04:00	04:00	0.24	4		6
3. 06:00	06:00	0.24	4		6
4. 08:00	08:00	0.24	4		6
5. 10:00	10:00	0.24	4		6
6. 12:00	12:00	0.24	4		6
7. 14:00	14:00	0.23	4		6
8. 16:00	16:00	0.22	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.24	4		6
12. 24:00	23:59	0.24	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 01:20 b. 05:00 c. 08:00 d. 21:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.24	4		6
4. 08:00	08:00	0.24	4		6
5. 10:00	10:00	0.23	4		6
6. 12:00	12:00	0.23	4		6
7. 14:00	14:00	0.25	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.23	4		6
10. 20:00	20:00	0.25	4		6
11. 22:00	22:00	0.25	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 01:00 b. 05:00 c. 08:00 d. 19:31

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.28	4		6
2. 04:00	04:00	0.24	4		6
3. 06:00	06:00	0.25	4		6
4. 08:00	08:00	0.25	4		6
5. 10:00	10:00	0.25	4		6
6. 12:00	12:00	0.29	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 01:51 b. 04:00 c. 20:00 d. 23:59

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.24	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	10:20	7.19	051	029	0.21	3	4		6
2. 16:00	15:55	7.25	044	039	0.21	2	4		6
3. 24:00									

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 04:00 b. 08:00 c. 20:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/03/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.21	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	22:00	0.21	4		6
12. 24:00	23:59	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:50	7.22	047	034	0.21	3	4		6
2. 16:00	09:10	7.21	043	155	0.21	1	4		6
3. 24:00	15:38	7.19	053	031	0.21	3	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 02:53 b. 07:30 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: MLD

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	06:00	0.21	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.30	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	03:10	7.26	048	034	0.21	3	4		6
2. 16:00	14:00	7.28	047	040	0.21	3	2		
3. 24:00	20:15	7.27	050	025	0.21	3	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 01:00 b. 05:00 c. 13:00 d. 20:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMC

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.23	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:59	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 00:00 b. 04:00 c. 12:00 d. 21:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMB

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.24	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.22	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.24	2		
7. 14:00	14:00	0.25	2		
8. 16:00	16:00	*.**	*		
9. 18:00	18:00	*.**	*		
10. 20:00	20:00	*.**	*		
11. 22:00	22:00	*.**	*		
12. 24:00	23:59	*.**	*		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 03:00 b. 09:00 c. 13:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMB

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	2		
2. 04:00	04:00	*.**	2		
3. 06:00	06:00	0.28	2		
4. 08:00	08:00	0.27	2		
5. 10:00	10:00	0.25	2		
6. 12:00	12:00	0.30	2		
7. 14:00	14:00	0.29	2		
8. 16:00	16:00	0.28	2		
9. 18:00	18:00	0.23	2		
10. 20:00	20:00	*.**	2		
11. 22:00	22:00	0.27	2		
12. 24:00	23:59	0.27	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 02:00 b. 09:00 c. 13:00 d. 17:00

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMB

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.27	2		
2. 04:00	04:00	*.**	*		
3. 06:00	06:00	*.**	*		
4. 08:00	08:00	*.**	*		
5. 10:00	10:00	*.**	*		
6. 12:00	12:00	0.24	2		
7. 14:00	14:00	0.27	2		
8. 16:00	16:00	0.27	2		
9. 18:00	18:00	*.**	*		
10. 20:00	20:00	*.**	*		
11. 22:00	22:00	*.**	*		
12. 24:00	23:59	*.**	*		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. 00:00 d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMB

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.23	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.25	2		
6. 12:00	12:00	0.25	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.23	2		
9. 18:00	18:00	0.25	2		
10. 20:00	20:00	*.**	*		
11. 22:00	22:00	*.**	*		
12. 24:00	23:59	*.**	*		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. 08:00 b. 12:00 c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: SMB

Form Completion Date: 03/19/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
02	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
03	(b) (6)	1	1	0	0	N	N	0	0	1	1	1	N	N	0	0		
04	(b) (6)	1	2	1	1	N	N	0	0	2	1	1	N	N	0	0		
05	(b) (6)	1	2	2	2	N	N	0	0	2	2	2	N	N	0	0		
06	(b) (6)	1	2	2	2	N	N	0	0	2	3	3	Y	Y	1	0		
07	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
08	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
09	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
10	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** . Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
11	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
12	(b) (6)	1	2	3	3	Y	N	1	0	2	3	3	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	015
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

Study Day	016
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	02:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	017
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	018
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	019
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	020
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	021
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/27/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	022
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	023
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	024
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	025
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	026
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	027
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** Birth No: 1

Study Day	028
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	029
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	030
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	031
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	032
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

Study Day	033
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	034
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	4
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	*
(b) Oxygen	*
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/27/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	035
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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Study Day	036
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	037
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	14:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	038
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	039
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	040
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** Birth No: 1

Study Day	041
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	13:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	042
Date:	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	02.000
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	043
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	044
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	045
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	046
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	047
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	048
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	049
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	050
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/27/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	051
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** Birth No: 1

Study Day	052
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	053
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	054
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	055
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

Study Day	056
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	09:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	21:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day	057
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	058
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	059
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	060
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

Study Day	061
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	5
(b) Oxygen	Y
(c) Flow Rate (NC Only)	01.500
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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Study Day	062
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	063
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	17:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day	064
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	05:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	11:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	7
(b) Oxygen	
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 065

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day 066

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day 067

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)
(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 068

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/27/2009

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Study Day 069

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 070

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** Birth No: 1

Study Day 071

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)
(a) Highest Level of Support (Mode) 9
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)
(a) Highest Level of Support (Mode)
(b) Oxygen
(c) Flow Rate (NC Only)
(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day 072

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

Study Day 073

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00
06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:
12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:
18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:
23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day 074

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

Study Day 075

Date (b) (6)
Month Day Year

1. Scheduled Time: 06:00

06:00 (time measured)

(a) Highest Level of Support (Mode) 9

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

2. Scheduled Time:

12:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

3. Scheduled Time:

18:00 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

4. Scheduled Time:

23:59 (time measured)

(a) Highest Level of Support (Mode)

(b) Oxygen

(c) Flow Rate (NC Only)

(d) Oximeter Alarm Check

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 03/19/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 28
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 03
   b. Parity: 03
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 6

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? Y
   a. If YES, Number of fetuses: 2
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? N
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? N

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? **N**

   a. If YES, were antibiotics given within 72 hrs prior to delivery?

   1. 3. 5.

   2. 4. 6.

4. Final mode of delivery: **3**

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) (Month Day Year) b. Time: **16:32** (Hour Min)

2. Was the infant outborn? **N**

   If YES, date and time admitted to NICU:

   a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? **N**

   IF YES, COMPLETE FORM NG03E

4. Sex: **2**

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: **2**

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: **2**

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: **25** b. Days: **0**

8. Apgar score - 1 minute: **05**

9. Apgar score - 5 minutes: **07**

10. Birth resuscitation/stabilization:

    a. Oxygen? **Y**

    b. Bagging and mask? **Y**

    c. CPAP? **N**

    d. Intubation? **Y**

    e. Chest compression? **N**

    f. Epinephrine? **N**

11. Birth Weight: (grams): **0800**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** Birth No: 1

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** Birth No: 1

12. Length (cm): 34.0
13. Head Circumference (cm): 23.0
14. Was cord blood gas done? Y

If Yes,

a. Cord pH (any vessel): 7.36
b. Base deficit (any vessel): **

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: 36.7
2. Fahrenheit:

a. Date: (b) (6) (Month Day Year)
b. Time: 17:05 (Hour Min)

c. Source: 2

1 = Rectal 2 = Axillary 3 = Skin

Initials of person completing this form: MLD

Form Completion Date: 09/10/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 1

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) [redacted] (Month Day Year)
3. Weight at status (grams): 1840
4. Length at status (cm): 45.0
5. Head circumference at status (cm): 31.7

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) [redacted] (Month Day Year) 16:45 (Hours Min)
   b. Total number of surfactant doses: 002
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: [redacted] (Month Day Year)
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure: [redacted]

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES, treatment:
   a. Indomethacin? N
   If YES, total number of courses
   b. Ibuprofin Y
   If YES, total number of courses 03
   c. Surgery? N

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? Y
   If YES,
   a. Date: (b) (6) [redacted] (Month Day Year) b. Time: 17:19 (Hour Min)
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? **Y**

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? **N**

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: (b) (6)
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area? **N**

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?	N	N
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?	N	N
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?	N	N
g. Blood/echo-density in the parenchyma?	N	N

4. Cystic area(s) in the parenchyma within 28 days? **N**

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? **Y**

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) **2**

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. [redacted] b. [redacted]
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 02
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? N
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: [redacted]
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0673
   b. Date of lowest weight in the first 10 days: (b) (6) [redacted]
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6) [redacted]

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2. Did the baby receive patenteral alimentation? **Y**

   If YES,

   a. Date of first patenteral alimentation (b) (6)

   b. Total number of days: **018**

3. Did the baby receive enteral feeds? **Y**

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? **Y**

      1) If YES, date first achieved: [redacted]

   c. Did the baby receive breast milk in the first 28 days? **Y**

      1) If YES, number of days baby received any breast milk in first 28 days: **18**

4. Proven NEC: **0**

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

   Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? **N**

   a. If YES, date of the first spontaneous gastrointestinal perforation:

   Month Day Year

6. Did the infant have GI surgery that resulted in short gut? **N**

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: *** , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **3**

1 = OAE	2 = AABR	3 = ABR	4 = OAE + AABR	5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

Results:	1. Pass	2. Fail	3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

Results:	1. Pass	2. Fail	3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **Y**

      2) Did plus disease develop in either eye? **N**

      3) Other therapies **N**

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **Y**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **1**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: *** , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

   1) = 2) = 3) =
   4) = 5) =

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: *** , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: **2**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) **1407**

c. Length (cm): **.*

d. Head circumference (cm) **.*

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply **1** **2**

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode: **1** **2**

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home: (b) (6)
Month Day Year

2. Discharged home on continuous oxygen? **N**

3. Discharged home on any of the following medications? **Y**

If YES,

a. Diuretics? **N**

b. Bronchodilators? **N**

c. Anticonvulsants? **N**

d. Antireflux medications? **Y**

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: *** , Birth No: 1

3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage
22 = RDS with infection                         Other
25 = BPD                                          60 = Immaturity
26 = BPD with infection                           90 = Other
27 = BPD with severe CNS insult                   99 = Unknown
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: SMC

Form Completion Date: 03/31/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: *** , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	00	00	00	000
2. On CV?	Y	N	2. Number of days on CV	2	2	08	16	16	016
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	24	024
4. On CPAP	N	N	4. Number days on CPAP	1	5	06	12	18	018
			5. Number of days on supplemental O2	3	7	14	28	56	056
6. FiO2	0.21	0.21	6. Highest FIO2 on day	0.27	0.24	0.25	0.25		0.25
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	N	N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?						

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FIO2                              4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)  6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)      9= Other-explain
```

Form Completion Date: 09/15/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

   0 = Not eligible
   1 = Consent granted
   2 = Parent unavailable
   3 = Parent refused consent
   4 = Consent not requested
   5 = Physician refused consent

   a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **04:23**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **2**

   1= Blue 2= Orange

Initials of person completing this form: **KAF**

SUPP02 Form Completion Date: **02/17/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: (b) (6) (Month Day Year) b. Time: 04:23 (Hour Min)

2. Was CPAP initiated in the DR? N

   If Yes, Date and time of CPAP initiation:

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Device:

   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other

   If (9) Other (specify device)

3. Was positive pressure ventilation (PPV) initiated in the DR? Y

4. Was positive and expiratory pressure (PEEP) used in the DR? Y

   If Yes,

   a. Maximum PEEP: 05

5. Was intubation attempted in the DR? Y

   If Yes, was the intubation successful? Y

6. Indication for intubation: 1

   1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR?

   b. Poor color?

   c. Apnea?

   d. Other?

   If Other specify:

   If (3) Other, specify:

7. Did the infant receive surfactant in the DR? Y

   If Yes, Date and time of administration:

   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

   c. Type: 1

   1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

8. Was active resuscitation required? **N**

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: **1**

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: **SMB**

SUPP03 Form Completion Date: **08/21/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 05:14 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2: ***

4. FiO2: 0.50

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 06:30 (Hour Min)

   c. Source: 1

      1= Arterial 2= Venous 3= Capillary

   d. pH: 7.21

   e. pCO2: 069

   f. pO2: 057

   g. FiO2: *.**

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

   c. Serial number: 311004

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

         1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

         If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year

b. Time: Hour Min

c. Source

1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	15:00	1
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KAF

SUPP04 Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**	*.**	*		
2. 04:00	05:00	0.50	2		
3. 06:00	06:45	0.30	2		
4. 08:00	08:00	0.26	2		
5. 10:00	10:00	0.23	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	23:25	0.21	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:45	7.26	029	086	*.**	1	2		
2. 16:00	16:20	7.51	022	090	*.**	1	2		
3. 24:00	22:45	7.48	023	070	*.**	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAP

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	00:56	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	**:**	*.**	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.33	2		
7. 14:00	14:00	0.23	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:05	7.38	025	***	*.**	1	2		
2. 16:00	13:45	7.24	024	***	*.**	1	2		
3. 24:00	20:30	7.22	022	***	*.**	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	08:50	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	13:05	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	**:**	*.**	2		
10. 20:00	20:00	0.21	2		
11. 22:00	20:37	0.21	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	12:30	7.29	021	071	*.**	1	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:13	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	07:30	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	**:**	*.**	4		6
12. 24:00	00:00	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:40	7.29	019	067	*.**	1	2		
2. 16:00	13:35	7.16	021	053	*.**	1	4		6
3. 24:00	20:55	7.30	021	054	*.**	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:15	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	**:**	*.**	4		6
4. 08:00	08:00	0.26	4		6
5. 10:00	10:00	0.26	4		6
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.23	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	**:**	*.**	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:15	7.28	021	042	*.**	1	4		6
2. 16:00	10:50	7.29	020	054	*.**	1	4		6
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:13	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:18	0.21	2		
4. 08:00	08:00	0.23	4		6
5. 10:00	11:00	0.22	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	13:54	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.24	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	20:08	0.22	4		6
12. 24:00	00:00	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	03:50	7.44	019	046	*.**	1	2		
2. 16:00	06:00	7.32	020	065	*.**	1	2		
3. 24:00	09:25	7.30	022	045	*.**	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.28	4		6
2. 04:00	04:00	0.28	4		6
3. 06:00	07:01	0.26	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.24	4		6
6. 12:00	12:00	0.26	4		6
7. 14:00	14:00	0.26	4		6
8. 16:00	16:00	0.26	4		6
9. 18:00	18:00	0.26	4		6
10. 20:00	20:00	0.24	4		6
11. 22:00	21:50	0.25	2		
12. 24:00	22:00	0.30	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	04:00	7.29	023	064	*.**	1	4		6
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	22:20	7.27	***	033	*.**	3	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

	a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1.	02:00	01:38	0.22	2		
2.	04:00	04:00	0.23	2		
3.	06:00	**:**	*.**	2		
4.	08:00	08:00	0.22	2		
5.	10:00	08:55	0.24	2		
6.	12:00	12:00	0.22	2		
7.	14:00	14:20	0.24	2		
8.	16:00	16:00	0.21	2		
9.	18:00	**:**	*.**	2		
10.	20:00	20:00	0.21	2		
11.	22:00	20:10	0.24	2		
12.	24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

	a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1.	08:00	03:55	7.23	***	033	*.**	3	2		
2.	16:00	16:03	7.25	***	033	*.**	3	2		
3.	24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:03	0.24	2		
2. 04:00	04:00	0.21	2		
3. 06:00	**:**	*.**	2		
4. 08:00	08:00	0.25	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.27	2		
7. 14:00	13:15	0.30	2		
8. 16:00	16:00	0.26	2		
9. 18:00	17:36	0.26	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.25	2		
12. 24:00	23:00	0.25	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	13:05	7.16	***	033	*.**	3	2		
2. 16:00	16:10	7.27	***	030	*.**	3	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.25	2		
3. 06:00	06:00	0.24	2		
4. 08:00	08:00	0.28	2		
5. 10:00	10:00	0.30	2		
6. 12:00	12:00	0.28	2		
7. 14:00	14:00	0.32	2		
8. 16:00	16:00	0.30	2		
9. 18:00	18:00	0.26	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.25	2		
12. 24:00	23:00	0.25	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	11:30	7.16	***	036	*.**	3	2		
2. 16:00	13:10	7.24	026	041	*.**	1	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	2		
2. 04:00	04:00	0.24	2		
3. 06:00	06:00	0.24	2		
4. 08:00	08:00	0.40	2		
5. 10:00	10:00	0.35	1		
6. 12:00	12:00	0.60	1		
7. 14:00	14:00	0.48	1		
8. 16:00	16:00	0.46	1		
9. 18:00	18:00	0.44	1		
10. 20:00	20:00	0.46	1		
11. 22:00	22:15	0.45	1		
12. 24:00	00:00	0.43	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:30	7.19	***	034	*.**	3	2		
2. 16:00	15:55	7.16	027	038	*.**	2	1		
3. 24:00	23:20	7.21	014	028	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:23	0.43	1		
2. 04:00	04:00	0.45	1		
3. 06:00	06:55	0.45	1		
4. 08:00	08:00	0.60	1		
5. 10:00	10:00	0.60	1		
6. 12:00	12:00	0.70	1		
7. 14:00	14:00	0.44	1		
8. 16:00	16:00	0.32	1		
9. 18:00	18:00	0.21	1		
10. 20:00	20:00	0.21	1		
11. 22:00	22:00	0.21	1		
12. 24:00	23:00	0.21	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:45	7.22	029	031	*.**	2	1		
2. 16:00	15:13	7.41	027	026	*.**	2	1		
3. 24:00	23:50	7.39	028	037	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	1		
2. 04:00	04:00	0.21	1		
3. 06:00	06:00	0.21	1		
4. 08:00	08:00	0.30	1		
5. 10:00	10:00	0.35	1		
6. 12:00	12:00	0.30	1		
7. 14:00	14:00	0.37	1		
8. 16:00	16:00	0.35	1		
9. 18:00	18:00	0.45	1		
10. 20:00	20:00	0.40	1		
11. 22:00	22:00	0.33	1		
12. 24:00	23:00	0.31	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:15	7.11	034	039	*.**	2	1		
2. 16:00	14:45	7.38	031	027	*.**	2	1		
3. 24:00	23:50	7.48	031	026	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.40	1		
2. 04:00	04:00	0.38	1		
3. 06:00	06:00	0.34	1		
4. 08:00	08:00	0.40	1		
5. 10:00	**:**	*.**	*		
6. 12:00	12:00	1.00	1		
7. 14:00	**:**	*.**	*		
8. 16:00	16:00	0.45	1		
9. 18:00	18:00	0.90	1		
10. 20:00	20:00	0.95	1		
11. 22:00	21:00	0.90	1		
12. 24:00	23:22	0.90	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	08:50	7.30	030	034	*.**	2	1		
2. 16:00	14:10	7.28	026	047	*.**	1	1		
3. 24:00	20:05	7.31	025	027	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
01	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
02	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
03	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
04	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N	0	0		
05	(b) (6)	1	1	1	1	Y	N	0	0	1	1	1	Y	N	0	0		
06	(b) (6)	1	1	3	3	N	N	1	0	1	3	3	N	N	1	0		
07	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
08	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
09	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
10	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient.

			Examination Results Left Eye							Examination Results Right Eye							STATUS ***	
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Final Acute Status Lost to Follow-up at 55 wks	Final ROP Status deter-mined at 18M Follow-Up
11	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
12	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0		
13	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N	0	0	N	

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

Study Day	015
Date	(b) (6) Month Day Year
1. Scheduled Time:	07:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	016
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	017
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	19:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	19:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	018
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	019
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	07:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	020
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	021
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	022
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	023
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	024
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	025
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	026
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	027
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	00:00

, Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	028
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: Birth No: 1

Study Day	029
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	030
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	031
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Study Day	032
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	033
Date	[redacted] (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	034
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	00:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	035
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	20:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	036
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	037
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	14:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	14:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	038
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	22:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/14/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	039
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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Study Day	040
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	041
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	042
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	043
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	15:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	044
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	045
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	046
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	01:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	047
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	01:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	048
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	14:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

Study Day	049
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	050
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: , Birth No: 1

Study Day	051
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 26
2. Maternal Zip Code: [redacted]
3. Pregnancy history (include this pregnancy):
   a. Gravida: 02
   b. Parity: 01
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 6

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? Y
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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3. Were maternal antibiotics used during the admission resulting in this delivery? **Y**

   a. If YES, were antibiotics given within 72 hrs prior to delivery? **U**

   1. 3. 5.

   2. 4. 6.

4. Final mode of delivery: **1**

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

   a. Date: (b) (6) Month Day Year

   b. Time: **04:23** Hour Min

2. Was the infant outborn? **N**

   If YES, date and time admitted to NICU:

   a. Date: Month Day Year

3. Did the infant die <= 12 hours? **N**

   IF YES, COMPLETE FORM NG03E

4. Sex: **1**

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: **2**

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: **2**

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

   a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: **25** b. Days: **1**

8. Apgar score - 1 minute: **03**

9. Apgar score - 5 minutes: **08**

10. Birth resuscitation/stabilization:

   a. Oxygen? **Y**

   b. Bagging and mask? **N**

   c. CPAP? **Y**

   d. Intubation? **Y**

   e. Chest compression? **N**

   f. Epinephrine? **N**

11. Birth Weight: (grams): **0770**

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~~Pt. Birth Weight (grams):~~

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

12. Length (cm): **31.0**

13. Head Circumference (cm): **23.0**

14. Was cord blood gas done? **N**

If Yes,

a. Cord pH (any vessel):

b. Base deficit (any vessel):

15. Was Infant's first temperature within 60 minutes of birth? **Y**

If Yes,

1. Centigrade: **36.5** 2. Fahrenheit:

a. Date: (b) (6) Month Day Year b. Time: ****:**** Hour Min

c. Source: **2**

1 = Rectal	2 = Axillary	3 = Skin

Initials of person completing this form: **KAF**

Form Completion Date: **09/11/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 2

```
1 = Discharged to home                    4 = Transferred to chronic care facility
2 = Still in hospital at 120 days         5 = Death
3 = Transferred to another hospital
```

2. Date of status: (b) (6) Month Day Year
3. Weight at status (grams): 1590
4. Length at status (cm): **.*
5. Head circumference at status (cm): 30.5

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) Month Day Year **:** Hours Min
   b. Total number of surfactant doses: 003
3. Pneumothorax? Y
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? Y
   a. If YES, Date of first dose: (b) (6) Month Day Year
6. Did infant receive inhaled nitric oxide? Y
   a. If YES, Date of first exposure: (b) (6)

C. CARDIAC

1. Patent ductus arteriosus (PDA)? N
   If YES, treatment:
   a. Indomethacin?
   If YES, total number of courses
   b. Ibuprofin
   If YES, total number of courses
   c. Surgery?

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? N
   If YES,
   a. Date: Month Day Year b. Time: Hour Min
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings:
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 2

   b. Date of image: (b) (6)
   Month Day Year

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: , Birth No: 1

c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 06
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 00
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0651
   b. Date of lowest weight in the first 10 days: (b)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

2. Did the baby receive patenteral alimentation? Y

If YES,

a. Date of first patenteral alimentation (b) (6)

b. Total number of days: 031

3. Did the baby receive enteral feeds? Y

If YES,

a. Date of first enteral feed: (b) (6)

b. Did enteral feeds reach 120 ml/kg/day? Y

1) If YES, date first achieved: (b) (6)

c. Did the baby receive breast milk in the first 28 days? Y

1) If YES, number of days baby received any breast milk in first 28 days: 02

4. Proven NEC: 0

0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

a. If proven NEC, Date of first episode?

Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? N

a. If YES, date of the first spontaneous gastrointestinal perforation:

Month Day Year

6. Did the infant have GI surgery that resulted in short gut? N

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? Y

   a. If YES, hearing screen protocol used: 3

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: 1

      ii) Left ear: 1

      Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

      Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? Y

   If Yes,

   a. Was ROP diagnosed in either eye? Y

      If Yes,

      1) Did it reach stage 3 or worse in either eye? Y

      2) Did plus disease develop in either eye? Y

      3) Other therapies N

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? Y

      2. Was any scleral buckle or vitrectomy performed in either eye? N

2. At the time of reaching status, indicate the most appropriate: 1

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: [redacted] SITENM: [redacted] Mother's Initials: , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: **2**

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) **0885**

c. Length (cm): ****.***

d. Head circumference (cm) ****.***

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home:
Month Day Year

2. Discharged home on continuous oxygen?

3. Discharged home on any of the following medications?

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage                                      Other
22 = RDS with infection                           60 = Immaturity
25 = BPD                                          90 = Other
26 = BPD with infection                           99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: SMC

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	04	18	38	038
2. On CV?	Y	N	2. Number of days on CV	3	7	10	10	31	031
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	00	000
4. On CPAP	N	Y	4. Number days on CPAP	0	0	00	00	06	006
			5. Number of days on supplemental O2	3	7	14	28	75	075
6. FiO2	0.21	0.21	6. Highest FIO2 on day	0.21	0.30	1.00	0.46		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	N	N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?	Y					N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation [redacted]

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field [redacted]

d. If on nasal cannula at time of challenge, record flow rate [redacted]

e. Did the patient pass the evaluation? [redacted]

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason: [redacted]

If 9, explain [redacted]

1= Increased FIO2
2= Increased respiratory support (cpap or vent)
3= Instability (including Surgery/Sepsis)
4= Parent/Physicial Refusal
6= Weaned to room air on/before day of evaluation
9= Other-explain

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? **Y**
2. Infant to receive full resuscitation as necessary? **Y**
3. Infant does not have known major congenital malformations? **Y**

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? **N**

   If Yes, indicate reason:

   1 = Equipment not available 2 = Personnel not available

C. CONSENT

1. Consent Status: **1**

0 = Not eligible	4 = Consent not requested
1 = Consent granted	5 = Physician refused consent
2 = Parent unavailable	
3 = Parent refused consent	

a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

D. RANDOMIZATION

1. Was infant randomized into the study? **Y**

   If No, indicate reason(s):

   If Yes,

   a. Date: (b) (6)
   Month Day Year

   b. Time: **04:23**
   Hour Min

   c. Randomization Number (b) (6)

   d. Treatment Assignment **1**

   1= Early Extubation and CPAP 2= Early Surfactant and Ventilation

   e. Oximeter Color Code: **2**

   1= Blue 2= Orange

Initials of person completing this form: **KAF**

SUPP02 Form Completion Date: **02/17/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:
   a. Date: (b) (6) (Month Day Year) b. Time: 04:23 (Hour Min)
2. Was CPAP initiated in the DR? N
   If Yes, Date and time of CPAP initiation:
   a. Date: (Month Day Year) b. Time: (Hour Min)
   c. Device:
   1 = Neopuff 2 = Ventilator 3 = Anesthesia Bag 4 = Bubble 9 = Other
   If (9) Other (specify device)
3. Was positive pressure ventilation (PPV) initiated in the DR? Y
4. Was positive and expiratory pressure (PEEP) used in the DR? Y
   If Yes,
   a. Maximum PEEP: 05
5. Was intubation attempted in the DR? Y
   If Yes, was the intubation successful? Y
6. Indication for intubation: 1

1=Surfactant administration 2=Resuscitation 3= Other (Specify) 4 = As required by randomization assignment

   If (2) Resuscitation,
   a. Low HR?
   b. Poor color?
   c. Apnea?
   d. Other?
   If Other specify:
   If (3) Other, specify:
7. Did the infant receive surfactant in the DR? Y
   If Yes, Date and time of administration:
   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)
   c. Type: 1

1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

   If (5) Other (specify type)

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

8. Was active resuscitation required? N

If Yes,

a. Chest compressions?

If Yes,

1. Duration: (Min)

b. Epinephrine?

If Yes,

1. Number of doses:

9. Status following resusciation: 1

1 = Admitted to NICU for further care
2 = Infant Died

Initials of person completing this form: SMB

SUPP03 Form Completion Date: 08/21/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

A. NICU ADMISSION

1. Date and time of NICU admission

   a. Date: (b) (6) (Month Day Year) b. Time: 05:14 (Hour Min)

2. Respiratory Support on admission to the NICU: 2

   1 = HVF 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

3. SaO2 ***

4. FiO2: 0.50

5. Was blood gas done after admission to the NICU? Y

   If Yes, record the first blood gas after admission:

   a. Date: (b) (6) (Month Day Year) b. Time: 06:30 (Hour Min)

   c. Source: 1

   1= Arterial 2= Venous 3= Capillary

   d. pH 7.21

   e. pCO2 069

   f. pO2 057

   g. FiO2 *.**

6. Date and time the study oximeter was placed on this infant.

   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)

   c. Serial number: 311004

B. NICU PROCEDURES

1. Was infant intubated for the first time within the first 14 days after admission to the NICU? N

   If Yes,

   a. Date: (Month Day Year) b. Time: (Hour Min)

   c. Indication for intubation:

      1. Surfactant?
      2. FiO2 > .50 to maintain SaO2 >= 88%
      3. pCO2 > 65 on single blood gas?
      4. Apnea requiring bag and mask ventilation?
      5. If NO to all above, state reason:

      1= Hemodynamic instability 2 = Clinical shock/sepsis 3 = Other

      If Other (3), specify

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete this question only if Q.B.1 is YES,

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes,

a. Date: Month Day Year b. Time: Hour Min

c. Source
1= Arterial 2= Venous 3= Capillary

d. pH

e. pCO2

f. pO2

g. FiO2

3. Was Surfactant given in the NICU? Y

If Yes, record the following for each dose: If more than 4 doses given see FORM SUPP04a

a) Dose#	b) Date:	c) Time:	d) Type:
1	(b) (6)	15:00	1
2			
3			
4			

*1 = Infasurf 2 = Curosurf 3 = Survanta 4 = Exosurf 5 = Other (Specify)

If Other (5), specify

Initials of person completing this form: KAF

SUPP04 Form Completion Date: 09/11/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Ver 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006
Revised October 15, 2007

CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 01 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	**:**	*.**	*		
2. 04:00	05:00	0.50	2		
3. 06:00	06:45	0.30	2		
4. 08:00	08:00	0.26	2		
5. 10:00	10:00	0.23	2		
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	23:25	0.21	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:45	7.26	029	086	*.**	1	2		
2. 16:00	16:20	7.51	022	090	*.**	1	2		
3. 24:00	22:45	7.48	023	070	*.**	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 02 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	00:56	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	**:**	*.**	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.33	2		
7. 14:00	14:00	0.23	2		
8. 16:00	16:00	0.21	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	22:00	0.21	2		
12. 24:00	23:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:05	7.38	025	***	*.**	1	2		
2. 16:00	13:45	7.24	024	***	*.**	1	2		
3. 24:00	20:30	7.22	022	***	*.**	1	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 03 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:00	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	08:50	0.21	2		
6. 12:00	12:00	0.21	2		
7. 14:00	13:05	0.21	2		
8. 16:00	16:00	0.21	2		
9. 18:00	**:**	*.**	2		
10. 20:00	20:00	0.21	2		
11. 22:00	20:37	0.21	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	**:**	*.**	***	***	*.**	*	*		
2. 16:00	12:30	7.29	021	071	*.**	1	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 04 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:13	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	07:30	0.21	2		
4. 08:00	08:00	0.21	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.21	4		6
7. 14:00	14:00	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.21	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	**:**	*.**	4		6
12. 24:00	00:00	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:40	7.29	019	067	*.**	1	2		
2. 16:00	13:35	7.16	021	053	*.**	1	4		6
3. 24:00	20:55	7.30	021	054	*.**	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alarm Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 05 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:15	0.21	4		6
2. 04:00	04:00	0.21	4		6
3. 06:00	**:**	*.**	4		6
4. 08:00	08:00	0.26	4		6
5. 10:00	10:00	0.26	4		6
6. 12:00	12:00	0.21	2		
7. 14:00	14:00	0.21	2		
8. 16:00	16:00	0.23	2		
9. 18:00	18:00	0.21	2		
10. 20:00	20:00	0.21	2		
11. 22:00	**:**	*.**	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	05:15	7.28	021	042	*.**	1	4		6
2. 16:00	10:50	7.29	020	054	*.**	1	4		6
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 06 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:13	0.21	2		
2. 04:00	04:00	0.21	2		
3. 06:00	06:18	0.21	2		
4. 08:00	08:00	0.23	4		6
5. 10:00	11:00	0.22	4		6
6. 12:00	12:00	0.21	4		6
7. 14:00	13:54	0.21	4		6
8. 16:00	16:00	0.21	4		6
9. 18:00	18:00	0.24	4		6
10. 20:00	20:00	0.21	4		6
11. 22:00	20:08	0.22	4		6
12. 24:00	00:00	0.21	4		6

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	03:50	7.44	019	046	*.**	1	2		
2. 16:00	06:00	7.32	020	065	*.**	1	2		
3. 24:00	09:25	7.30	022	045	*.**	1	4		6

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 07 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.28	4		6
2. 04:00	04:00	0.28	4		6
3. 06:00	07:01	0.26	4		6
4. 08:00	08:00	0.21	4		6
5. 10:00	10:00	0.24	4		6
6. 12:00	12:00	0.26	4		6
7. 14:00	14:00	0.26	4		6
8. 16:00	16:00	0.26	4		6
9. 18:00	18:00	0.26	4		6
10. 20:00	20:00	0.24	4		6
11. 22:00	21:50	0.25	2		
12. 24:00	22:00	0.30	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	04:00	7.29	023	064	*.**	1	4		6
2. 16:00	**:**	*.**	***	***	*.**	*	*		
3. 24:00	22:20	7.27	***	033	*.**	3	2		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? Y

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 08 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:38	0.22	2		
2. 04:00	04:00	0.23	2		
3. 06:00	**:**	*.**	2		
4. 08:00	08:00	0.22	2		
5. 10:00	08:55	0.24	2		
6. 12:00	12:00	0.22	2		
7. 14:00	14:20	0.24	2		
8. 16:00	16:00	0.21	2		
9. 18:00	**:**	*.**	2		
10. 20:00	20:00	0.21	2		
11. 22:00	20:10	0.24	2		
12. 24:00	00:00	0.21	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	03:55	7.23	***	033	*.**	3	2		
2. 16:00	16:03	7.25	***	033	*.**	3	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 09 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:03	0.24	2		
2. 04:00	04:00	0.21	2		
3. 06:00	**:**	*.**	2		
4. 08:00	08:00	0.25	2		
5. 10:00	10:00	0.21	2		
6. 12:00	12:00	0.27	2		
7. 14:00	13:15	0.30	2		
8. 16:00	16:00	0.26	2		
9. 18:00	17:36	0.26	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.25	2		
12. 24:00	23:00	0.25	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	13:05	7.16	***	033	*.**	3	2		
2. 16:00	16:10	7.27	***	030	*.**	3	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 10 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	2		
2. 04:00	04:00	0.25	2		
3. 06:00	06:00	0.24	2		
4. 08:00	08:00	0.28	2		
5. 10:00	10:00	0.30	2		
6. 12:00	12:00	0.28	2		
7. 14:00	14:00	0.32	2		
8. 16:00	16:00	0.30	2		
9. 18:00	18:00	0.26	2		
10. 20:00	20:00	0.25	2		
11. 22:00	22:00	0.25	2		
12. 24:00	23:00	0.25	2		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	11:30	7.16	***	036	*.**	3	2		
2. 16:00	13:10	7.24	026	041	*.**	1	2		
3. 24:00	**:**	*.**	***	***	*.**	*	*		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 11 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.23	2		
2. 04:00	04:00	0.24	2		
3. 06:00	06:00	0.24	2		
4. 08:00	08:00	0.40	2		
5. 10:00	10:00	0.35	1		
6. 12:00	12:00	0.60	1		
7. 14:00	14:00	0.48	1		
8. 16:00	16:00	0.46	1		
9. 18:00	18:00	0.44	1		
10. 20:00	20:00	0.46	1		
11. 22:00	22:15	0.45	1		
12. 24:00	00:00	0.43	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:30	7.19	***	034	*.**	3	2		
2. 16:00	15:55	7.16	027	038	*.**	2	1		
3. 24:00	23:20	7.21	014	028	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 12 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	01:23	0.43	1		
2. 04:00	04:00	0.45	1		
3. 06:00	06:55	0.45	1		
4. 08:00	08:00	0.60	1		
5. 10:00	10:00	0.60	1		
6. 12:00	12:00	0.70	1		
7. 14:00	14:00	0.44	1		
8. 16:00	16:00	0.32	1		
9. 18:00	18:00	0.21	1		
10. 20:00	20:00	0.21	1		
11. 22:00	22:00	0.21	1		
12. 24:00	23:00	0.21	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	07:45	7.22	029	031	*.**	2	1		
2. 16:00	15:13	7.41	027	026	*.**	2	1		
3. 24:00	23:50	7.39	028	037	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 13 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.21	1		
2. 04:00	04:00	0.21	1		
3. 06:00	06:00	0.21	1		
4. 08:00	08:00	0.30	1		
5. 10:00	10:00	0.35	1		
6. 12:00	12:00	0.30	1		
7. 14:00	14:00	0.37	1		
8. 16:00	16:00	0.35	1		
9. 18:00	18:00	0.45	1		
10. 20:00	20:00	0.40	1		
11. 22:00	22:00	0.33	1		
12. 24:00	23:00	0.31	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	09:15	7.11	034	039	*.**	2	1		
2. 16:00	14:45	7.38	031	027	*.**	2	1		
3. 24:00	23:50	7.48	031	026	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode Support 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: EJB

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Complete a form each day through DOL 14

1. Study Day 14 **2. Date** (b) (6)

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time	b. Time Measured (hour : min)	f. FiO2	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 02:00	02:00	0.40	1		
2. 04:00	04:00	0.38	1		
3. 06:00	06:00	0.34	1		
4. 08:00	08:00	0.40	1		
5. 10:00	**:**	*.**	*		
6. 12:00	12:00	1.00	1		
7. 14:00	**:**	*.**	*		
8. 16:00	16:00	0.45	1		
9. 18:00	18:00	0.90	1		
10. 20:00	20:00	0.95	1		
11. 22:00	21:00	0.90	1		
12. 24:00	23:22	0.90	1		

4. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO2	g. Source*	h. Mode of Support**	i. If Mode = 5 record flow rate	j. If Mode = 4 (CPAP) Type Used***
1. 08:00	08:50	7.30	030	034	*.**	2	1		
2. 16:00	14:10	7.28	026	047	*.**	1	1		
3. 24:00	20:05	7.31	025	027	*.**	2	1		

*Source 1 = Arterial 2 = Venous 3 = Capillary

**Mode 1 = HFV 2 = CV 3 = Nasal SIMV 4 = CPAP 5 = NC 6 = Hood 7 = No Support

***CPAP Type 2=Ventilator 5=Bubble 6=Flow Driver 9=Other

5. Oximeter Alam Check (record every 6 hours)

a. **:** b. **:** c. **:** d. **:**

6. Was the Infant intubated or extubated on this day? N

If Yes, complete the SUPP05A

Initials of person completing this form: KAF

Form Completion Date: 09/11/2009

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials:

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a ba outpatient.

			Examination Results Left Eye							Examination Re: Right Eye				
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)
01	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N
02	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N
03	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N
04	(b) (6)	1	1	0	0	N	N	0	0	1	0	0	N	N
05	(b) (6)	1	1	1	1	Y	N	0	0	1	1	1	Y	N
06	(b) (6)	1	1	3	3	N	N	1	0	1	3	3	N	N
07	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N
08	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N
09	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N
10	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

CENTER: 19 NETWORK (b) (6) SITENM (b) (6) Mother's Initials: ,

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a ba outpatient.

			Examination Results Left Eye							Examination Re: Right Eye				
	Date of Exam	Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)	Surg-ery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage in any Zone	"Plus Disease"	Threshold (New Type I)
11	(b) (6)	1	5	6	6	N	N	0	0	5	6	6	N	N
12	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N
13	(b) (6)	2	5	6	6	N	N	0	0	5	6	6	N	N

LOCATION: 1 = Inpatient 2 = Outpatient 3 = Transfer Hospital

*ZONE: 1 = I 2 = II 3 = III 4 = Mature 5 = Status post laser/cryo 9 = Unable to determine

+STAGE: 0 = No ROP
1 = Stage 1
2 = Stage 2
3 = Stage 3
4 = Stage 4a or 4b
5 = Stage 5
6 = Post laser/cryo (do not use stages)
9 = Old scars, but no active ROP

^ SURGERY: 0 = No surgery this day
1 = Laser
2 = Cryotherapy
3 = Both laser/cryo
4 = Scleral buckle
5 = Vitrectomy
6 = Other

**RETINAL DETACHMENT:
0 = None
3 = Partial, not involving macula (stage 4a)
4 = Partial, does involve macula (stage 4b)
5 = Complete
9 = View obscured, can't tell

*** only answer these questions for the last eye exam entered

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	015
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	07:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	016
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	017
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	19:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	19:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

Study Day	018
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:59

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	019
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	07:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	020
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	**021**
Date	(b) (6) Month Day Year
1. Scheduled Time:	**06:00**
06:00	(time measured)
(a) Highest Level of Support (Mode)	**1**
(b) Oxygen	**Y**
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**06:00**
2. Scheduled Time:	**12:00**
12:00	(time measured)
(a) Highest Level of Support (Mode)	**1**
(b) Oxygen	**Y**
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**12:00**
3. Scheduled Time:	**18:00**
18:00	(time measured)
(a) Highest Level of Support (Mode)	**1**
(b) Oxygen	**Y**
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**18:00**
4. Scheduled Time:	**23:00**
23:59	(time measured)
(a) Highest Level of Support (Mode)	**1**
(b) Oxygen	**Y**
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**23:00**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: **09/11/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	022
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	023
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	024
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: Birth No: 1

Study Day	025
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	026
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	027
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	00:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	028
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	029
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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Study Day	030
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	031
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	032
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	033
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	034
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	00:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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Study Day	035
Date	(b) (6)
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	20:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	036
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	18:00
4. Scheduled Time:	23:00
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	23:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

Study Day	037
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	07:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	14:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	14:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	038
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	22:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

Study Day	039
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	06:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	040
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	041
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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Study Day	042
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	16:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	043
Date	(b) (6) (Month Day Year)
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	15:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	044
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	045
Date	(b) (6) [redacted]
	Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	2
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

Study Day	046
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	01:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	12:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: Birth No: 1

Study Day	047
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	01:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	048
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	14:00
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	049
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	08:00
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

Study Day	050
Date	(b) (6) [redacted] Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	04:00
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

Study Day	051
Date	(b) (6) Month Day Year
1. Scheduled Time:	06:00
06:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
2. Scheduled Time:	12:00
12:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
3. Scheduled Time:	18:00
18:00	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	**:**
4. Scheduled Time:	23:59
23:59	(time measured)
(a) Highest Level of Support (Mode)	1
(b) Oxygen	Y
(c) Flow Rate (NC Only)	
(d) Oximeter Alarm Check	20:00

** Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7=No Support 8= Infant temporarily out of unit 9 = No Support all day and not on study oximeter

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 26
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy): (6)
   a. Gravida: 02
   b. Parity: 01
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 6

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? Y
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? N
   If Yes,
   a. Date: Month Day Year
   b. Time: Hour Min
   c. If date and/or time unknown, were ROM estimated at > 18 hours?
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? Y

a. If YES, were antibiotics given within 72 hrs prior to delivery? U

1. 3. 5.

2. 4. 6.

4. Final mode of delivery: 1

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

a. Date: (b) (6) (Month Day Year) b. Time: 04:23 (Hour Min)

2. Was the infant outborn? N

If YES, date and time admitted to NICU:

a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

IF YES, COMPLETE FORM NG03E

4. Sex: 1

1 = Male	2 = Female	3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 2

1 = Black	5 = Native Hawaiian or Other Pacific Islander
2 = White	6 = More Than One Race
3 = American Indian or Alaska Native	7 = Unknown or Not Reported
4 = Asian	

a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 25 b. Days: 1

8. Apgar score - 1 minute: 03

9. Apgar score - 5 minutes: 08

10. Birth resuscitation/stabilization:

a. Oxygen? Y

b. Bagging and mask? N

c. CPAP? Y

d. Intubation? Y

e. Chest compression? N

f. Epinephrine? N

11. Birth Weight (grams): 0770

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: Birth No: 1

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

12. Length (cm): **31.0**
13. Head Circumference (cm): **23.0**
14. Was cord blood gas done? **N**

If Yes,

a. Cord pH (any vessel):
b. Base deficit (any vessel):

15. Was Infant's first temperature within 60 minutes of birth? **Y**

If Yes,

1. Centigrade: **36.5**
2. Fahrenheit:

a. Date: (b) (6) (Month Day Year)
b. Time: ****:**** (Hour Min)

c. Source: **2**

1 = Rectal 2 = Axillary 3 = Skin

Initials of person completing this form: **KAF**

Form Completion Date: **09/11/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: **2**

1 = Discharged to home
2 = Still in hospital at 120 days
3 = Transferred to another hospital
4 = Transferred to chronic care facility
5 = Death

2. Date of status: (b) (6) (Month Day Year)
3. Weight at status (grams): **1590**
4. Length at status (cm): ****.***
5. Head circumference at status (cm): **30.5**

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? **Y**
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? **Y**
2. Did the baby receive surfactants? **Y**
   a. If YES, date and time of first dose: (b) (6) (Month Day Year) ****:**** (Hours Min)
   b. Total number of surfactant doses: **003**
3. Pneumothorax? **Y**
4. Pulmonary hemorrhage? **N**
5. Steroids for BPD/CLD? **Y**
   a. If YES, Date of first dose: (b) (6) (Month Day Year)
6. Did infant receive inhaled nitric oxide? **Y**
   a. If YES, Date of first exposure: (b) (6)

C. CARDIAC

1. Patent ductus arteriosus (PDA)? **N**
   If YES, treatment:
   a. Indomethacin?
   If YES, total number of courses
   b. Ibuprofin
   If YES, total number of courses
   c. Surgery?

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? **N**
   If YES,
   a. Date: (Month Day Year) b. Time: (Hour Min)
2. Were there seizures treated with an anti-convulsant for >72 hours? **N**

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3. Were any cranial sonograms done within 28 days of birth? Y

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? Y

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings:
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area?

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?		
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?		
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?		
g. Blood/echo-density in the parenchyma?		

4. Cystic area(s) in the parenchyma within 28 days?

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? Y

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) 2

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 06
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? Y
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days: 00
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1				
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0651
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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2. Did the baby receive patenteral alimentation? **Y**

   If YES,

   a. Date of first patenteral alimentation **(b) (6)**

   b. Total number of days: **031**

3. Did the baby receive enteral feeds? **Y**

   If YES,

   a. Date of first enteral feed: **(b) (6)**

   b. Did enteral feeds reach 120 ml/kg/day? **Y**

      1) If YES, date first achieved: **(b) (6)**

   c. Did the baby receive breast milk in the first 28 days? **Y**

      1) If YES, number of days baby received any breast milk in first 28 days: **02**

4. Proven NEC: **0**

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

   Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? **N**

   a. If YES, date of the first spontaneous gastrointestinal perforation:

   Month Day Year

6. Did the infant have GI surgery that resulted in short gut? **N**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **3**

   1 = OAE 2 = AABR 3 = ABR 4 = OAE + AABR 5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

   Results: 1. Pass 2. Fail 3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

   Results: 1. Pass 2. Fail 3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **Y**

      2) Did plus disease develop in either eye? **Y**

      3) Other therapies **N**

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **Y**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **1**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

1. Determined Favorable:
   - Vessels mature (fully vascularized)
   - Vessels in zone III for two consecutive exams
   - ROP of stage 1 or 2 in zone III for two consecutive exams
   - ROP in zone II or zone III but determined to be clearly regressing

2. Determined-Severe:
   - ROP surgery
   - Retinal detachment
   - Avastin injection

3. Undetermined:
   - Immature Vessels in zone I and II
   - Immature Vessels reaching zone III for only 1 exam
   - Stage 1 or 2 ROP in zone III for only 1 exam
   - Stage 3 ROP in zone III
   - ROP in zone I or zone II
   - Plus disease

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CENTER: 19 NETWORK: (b) (6) SITENM: [redacted] Mother's Initials: , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? N

   a. If YES, code:

   1) = | 2) = | 3) =
   4) = | 5) =

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? N

   a. If YES, code:

   1) = | 2) = | 3) =
   4) = | 5) =

   i) If a major surgery is coded 999, specify:

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K. 36 WEEK INFORMATION

1. Status at 36 weeks: 2

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) 0885

c. Length (cm): **.*

d. Head circumference (cm) **.*

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode:

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home:
Month Day Year

2. Discharged home on continuous oxygen?

3. Discharged home on any of the following medications?

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage                                      Other
22 = RDS with infection                           60 = Immaturity
25 = BPD                                          90 = Other
26 = BPD with infection                           99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: SMC

Form Completion Date: 09/11/2009

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	04	18	38	038
2. On CV?	Y	N	2. Number of days on CV	3	7	10	10	31	031
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	00	000
4. On CPAP	N	Y	4. Number days on CPAP	0	0	00	00	06	006
			5. Number of days on supplemental O2	3	7	14	28	75	075
6. FiO2	0.21	0.21	6. Highest FIO2 on day	0.21	0.30	1.00	0.46		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.	N	N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?	Y					N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FI02                                  4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)    6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)          9= Other-explain
```

Form Completion Date: **09/11/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. MATERNAL INFORMATION

1. Mother's age (years): 29
2. Maternal Zip Code: (b) (6)
3. Pregnancy history (include this pregnancy):
   a. Gravida: 03
   b. Parity: 02
4. Marital Status: 1

1 = Married	2 = Single	6 = Unknown

5. Highest level of education achieved by the Biological Mother: 8

1 = < 7th grade	5 = Partial college
2 = 7th to 9th grade	6 = College degree
3 = 10th to 12th grade	7 = Graduate degree
4 = High School degree	8 = Unknown

6. Mother's medical insurance: 3

1 = Medicaid	6 = Unknown
3 = Private	9 = Other
5 = Self-pay/uninsured	

B. PREGNANCY COMPLICATIONS

1. Multiple birth? N
   a. If YES, Number of fetuses:
2. Mother has evidence of at least one prenatal visit in this pregnancy? Y
3. Diabetes - insulin dependent? N
   If YES, was insulin given prior to pregnancy?
4. Hypertension? N
   a. Hypertension existed prior to pregnancy?
5. Antepartum hemorrhage? N
6. Was Chorioamnionitis documented in the mother's medical record? Y
7. Was a placental pathology performed? Y
   If YES,
   a. Was histologic chorioamnionitis documented? Y

C. LABOR AND DELIVERY

1. Was there a rupture of membranes prior to delivery? Y
   If Yes,
   a. Date: (b) (6) (Month Day Year) b. Time: **:** (Hour Min)
   c. If date and/or time unknown, were ROM estimated at > 18 hours? Y
2. Were steroids given prior to delivery to accelerate maturity? Y
   a. If YES, Type of antenatal steroid given: 1

1 = Betamethasone	2 = Dexamethasone	3 = Both	4 = UK

   b. Was a complete course of steriods given prior to delivery? Y

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: Birth No: 1

3. Were maternal antibiotics used during the admission resulting in this delivery? Y

a. If YES, were antibiotics given within 72 hrs prior to delivery? Y

1. 01 3. 5.

2. 68 4. 6.

4. Final mode of delivery: 3

1 = Vaginal vertex	2 = Vaginal breech	3 = Cesarean section	4 = Vaginal NOS	5 = Unknown

D. NEONATAL INFORMATION

1. Date and time of birth:

a. Date: (b) (6) (Month Day Year) b. Time: 00:21 (Hour Min)

2. Was the infant outborn? N

If YES, date and time admitted to NICU:

a. Date: (Month Day Year)

3. Did the infant die <= 12 hours? N

IF YES, COMPLETE FORM NG03E

4. Sex: 2

1 = Male 2 = Female 3 = Ambiguous

5. Ethnic Categories: 2

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or Not Reported

6. Racial Categories: 1

1 = Black
2 = White
3 = American Indian or Alaska Native
4 = Asian
5 = Native Hawaiian or Other Pacific Islander
6 = More Than One Race
7 = Unknown or Not Reported

a. If coding option 6, record all races indicated (optional)

7. Gestational age: a. Weeks: 25 b. Days: 2

8. Apgar score - 1 minute: 06

9. Apgar score - 5 minutes: 07

10. Birth resuscitation/stabilization:

a. Oxygen? Y

b. Bagging and mask? N

c. CPAP? N

d. Intubation? Y

e. Chest compression? N

f. Epinephrine? N

11. Birth Weight: (grams): 0800

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) Mother's Initials: , Birth No: 1

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: Birth No: 1

12. Length (cm): 33.0
13. Head Circumference (cm): 24.0
14. Was cord blood gas done? Y

If Yes,

a. Cord pH (any vessel): 7.38
b. Base deficit (any vessel): **

15. Was Infant's first temperature within 60 minutes of birth? Y

If Yes,

1. Centigrade: 36.6
2. Fahrenheit:

a. Date: (b) (6) (Month Day Year)
b. Time: 00:45 (Hour Min)

c. Source: 2

1 = Rectal 2 = Axillary 3 = Skin

Initials of person completing this form: KRF

Form Completion Date: 05/27/2009

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

A. STATUS

1. Status of infant at time of completion of form: 1

1 = Discharged to home	4 = Transferred to chronic care facility
2 = Still in hospital at 120 days	5 = Death
3 = Transferred to another hospital	

2. Date of status: (b) (6) (Month Day Year)
3. Weight at status (grams): 2045
4. Length at status (cm): 40.0
5. Head circumference at status (cm): 33.0

B. PULMONARY

1. Respiratory distress:
   a. Demonstrated clinical features of respiratory distress within the first 24 hrs? Y
   b. Required oxygen or postive pressure for more than 6 hours within the first 24 hours? Y
2. Did the baby receive surfactants? Y
   a. If YES, date and time of first dose: (b) (6) (Month Day Year) 00:25 (Hours Min)
   b. Total number of surfactant doses: 003
3. Pneumothorax? N
4. Pulmonary hemorrhage? N
5. Steroids for BPD/CLD? N
   a. If YES, Date of first dose: (Month Day Year)
6. Did infant receive inhaled nitric oxide? N
   a. If YES, Date of first exposure:

C. CARDIAC

1. Patent ductus arteriosus (PDA)? Y
   If YES, treatment:
   a. Indomethacin? N
   If YES, total number of courses
   b. Ibuprofin Y
   If YES, total number of courses 01
   c. Surgery? N

D. NEUROLOGIC

1. Was indomethacin given within the first 24 hrs for any prophylaxis? N
   If YES,
   a. Date: (Month Day Year) b. Time: (Hour Min)
2. Were there seizures treated with an anti-convulsant for >72 hours? N

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3. Were any cranial sonograms done within 28 days of birth? **Y**

   If NO, Go to Question D5

   a. If Yes, Were all studies without evidence of intracranial hemorrhage, peri-ventricular leukomalacia or ventriculomegaly? **N**

   If Yes, Go to Question D5

   b. Date of sonogram for most severe findings: (b) (6)
   Month Day Year

   c. Blood/echodensity in germinal matrix/subependymal area? **Y**

	(1) RIGHT	(2) LEFT
d. Blood/echodensity in the ventricle?	N	N
e. Ventricular size enlarged with concurrent or prior blood in the ventricles?	N	N
f. Ventricular size enlarged without concurrent or prior blood in the ventricles?	N	N
g. Blood/echo-density in the parenchyma?	N	N

4. Cystic area(s) in the parenchyma within 28 days? **N**

   If YES,

	(1) RIGHT	(2) LEFT
a. Cystic periventricular leukomalacia within 28 days?		
b. Porencephalic cyst within 28 days?		

5. Were any cranial imaging studies done after 28 days of birth? **Y**

   If NO, Go to Section E.

6. Cranial sonogram closest to 36 weeks postmenstrual age and after 28 days of birth:

   a. Type of imaging (1=MRI, 2=Sonogram, 3=CT scan) **2**

   b. Date of image: (b) (6)
   Month Day Year

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c. Normal study? Y

If NO,

	(1) RIGHT	(2) LEFT
d. Ventricular size enlarged?		
e. Cystic periventricular leukomalacia?		
f. Porencephalic cyst?		

E. INFECTIO

1. Early onset septicemia/bacteremia at (<= 72 hours)? N
   If YES, organism code(s): a. [redacted] b.
2. Did the infant receive antibiotics for >= 5 days, starting within the first 72 hours? Y
3. Number of episodes of late onset blood culture negative clinical infection (>=72 hours to status) treated with antibiotics for >= 5 days: 01
4. Late onset culture positive septicemia/bacteremia (>= 72 hours)? N
   If YES,
   a. Number of episodes between day 3 and status that were treated with antibiotics for >= 5 days:
   b. Organism code(s) and date of first positive culture for each of episodes for which the infant was treated with antibiotics for >= 5 days:

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	[redacted]			
2				
3				
4				
5				
6				

5. Meningitis? N
   a. If YES,

a)Episode#	(b) Date	(1) Organism	(2) Organism	(3) Organism
1	[redacted]			
2				

F. GASTROINTESTINAL

1. Did weight ever fall below the birth weight during the first 10 days? Y
   If YES,
   a. Lowest weight in the first 10 days? 0635
   b. Date of lowest weight in the first 10 days: (b) (6)
   c. Was birth weight regained? Y
   If YES
   d. Date birth weight first regained: (b) (6)

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2. Did the baby receive patenteral alimentation? **Y**

   If YES,

   a. Date of first patenteral alimentation (b) (6)

   b. Total number of days: **043**

3. Did the baby receive enteral feeds? **Y**

   If YES,

   a. Date of first enteral feed: (b) (6)

   b. Did enteral feeds reach 120 ml/kg/day? **Y**

      1) If YES, date first achieved: (b) (6)

   c. Did the baby receive breast milk in the first 28 days? **Y**

      1) If YES, number of days baby received any breast milk in first 28 days: **03**

4. Proven NEC: **0**

   0 = Absent/Suspect 2 = Proved, no surgery 3 = Proved, surgery

   a. If proven NEC, Date of first episode?

   Month Day Year

5 Spontaneous gastrointestinal perforation without proven NEC? **N**

   a. If YES, date of the first spontaneous gastrointestinal perforation:

   Month Day Year

6. Did the infant have GI surgery that resulted in short gut? **N**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b) (6) Mother's Initials: , Birth No: 1

G. HEARING

1. Was a Hearing screen performed? **Y**

   a. If YES, hearing screen protocol used: **5**

1 = OAE	2 = AABR	3 = ABR	4 = OAE + AABR	5 = Other

   b. Final screen results before discharge

      i) Right ear: **1**

      ii) Left ear: **1**

Results:	1. Pass	2. Fail	3. Incomplete

   c. If a failed screen in either ear, was a diagnostic ABR done prior to status?

      1) If YES, answer the following:

         i) Right ear:

         ii) Left ear:

Results:	1. Pass	2. Fail	3. Incomplete

H. OPHTHALMOLOGY

1. Was an exam performed for ROP? **Y**

   If Yes,

   a. Was ROP diagnosed in either eye? **Y**

      If Yes,

      1) Did it reach stage 3 or worse in either eye? **N**

      2) Did plus disease develop in either eye? **N**

      3) Other therapies **N**

         (if yes, specify):

   b. Intervention Therapies:

      1. Was retinal ablation performed in either eye (laser and/or cryotherapy)? **N**

      2. Was any scleral buckle or vitrectomy performed in either eye? **N**

2. At the time of reaching status, indicate the most appropriate: **3**

   1 = Determined, favorable in both eyes

   2 = Determined, severe ROP in either eye

   3 = Undetermined ROP status in either eye (and neither had "severe ROP")

```
1. Determined Favorable:
   -    Vessels mature (fully vascularized)
   -    Vessels in zone III for two consecutive exams
   -    ROP of stage 1 or 2 in zone III for two consecutive exams
   -    ROP in zone II or zone III but determined to be clearly regressing
```

```
2.  Determined-Severe:
    -    ROP surgery
    -    Retinal detachment
    -    Avastin injection
```

```
3.  Undetermined:
    -    Immature Vessels in zone I and II
    -    Immature Vessels reaching zone III for only 1 exam
    -    Stage 1 or 2 ROP in zone III for only 1 exam
    -    Stage 3 ROP in zone III
    -    ROP in zone I or zone II
    -    Plus disease
```

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CENTER: 19 NETWORK: (b) (6) SITENM (b) (6) Mother's Initials: , Birth No: 1

I. SYNDROMES

1. Syndromes and/or major malformations? **N**

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   b) If a syndrome is coded "699", specify:

J. MAJOR SURGERY

1. Other major surgery not covered in previous sections? **N**

   a. If YES, code:

1) =	2) =	3) =
4) =	5) =	

   i) If a major surgery is coded 999, specify:

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CENTER: 19 NETWORK: (b) (6) SITENM(b) (6) Mother's Initials: , Birth No: 1

K. 36 WEEK INFORMATION

1. Status at 36 weeks: 2

1 = Discharged 2 = In hospital 3 = Transferred 5 = Death

If "2", (In Hospital):

a. Date of 36 weeks measurement: (b) (6)
Month Day Year

b. Weight (g) ****

c. Length (cm): **.*

d. Head circumference (cm) **.*

L. FEEDING STATUS:

1. Type of nutrition at discharge to home. Code all that apply 1 2

(Do not complete for transfer patients):

1 = Breastmilk 2 = Formula 3 = TPN

2. If enteral, Mode: 1 2

1 = Breast 2 = Bottle 3 = NG/NJ tube 4 = Gastrostomy tube 9 = Unknown

M. TRANSFER

Complete this section if status (AI) of infant at time of completion of this form is "3" or "4".

1. Date of transfer:
Month Day Year

2. Final outcome:

1 = Died in Hospital 2 = Discharged to Home 6 = Remains in hospital at one year

a. If discharged to home, final weight at discharge (grams):

N. DISCHARGE ALIVE

Complete this section if status (Q. A1 above) of infant at time of completion of this form is "1" or if the final outcome for a transferred infant is 'Discharged to home.'

1. Date of discharge to home: (b) (6)
Month Day Year

2. Discharged home on continuous oxygen? N

3. Discharged home on any of the following medications? N

If YES,

a. Diuretics?

b. Bronchodilators?

c. Anticonvulsants?

d. Antireflux medications?

O. DEATH

1. Date of Death:
Month Day Year

a. Time of Death
Hours Minutes

2. Autopsy performed?

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CENTER: 19 NETWORK: (b) (6) SITENM (b) Mother's Initials: , Birth No: 1

3. Contributory Cause of death

```
Malformation                                    NEC
10 = Congenital malformation                      40 = NEC
Pulmonary                                         41 = NEC with sepsis
20 = RDS                                        CNS Insult
21 = RDS with severe intracranial hemorrhage      50 = Severe intracranial
hemorrhage                                      Other
22 = RDS with infection                           60 = Immaturity
25 = BPD                                          90 = Other
26 = BPD with infection                           99 = Unknown
27 = BPD with severe CNS insult
Infection
30 = Suspect sepsis/infection
31 = Proven sepsis/infection
```

4. If contributory cause of death is code "10" (Congenital malformation), or code "90" (other), specify:

5. Was respiratory support withheld or withdrawn at any time prior to death?

Initials of person completing this form: **SMC**

Form Completion Date: **05/20/2009**

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CENTER: 19 NETWORK: (b) (6) SITENM: (b)(6) Mother's Initials: , Birth No: 1

A. SNAPSHOT	@ 24 HOUR	@ 36 WEEKS	B. CUMULATIVE DATA	DAY 3	DAY 7	DAY 14	DAY 28	36 WEEK	STATUS
1. On HFV?	N	N	1. Number days on HFV	0	0	00	00	00	000
2. On CV?	Y	N	2. Number of days on CV	3	4	04	06	06	006
3. On nasal SIMV?	N	N	3. Number of days on nasal SIMV	0	0	00	00	19	019
4. On CPAP	N	N	4. Number days on CPAP	0	3	10	18	18	018
			5. Number of days on supplemental O2	3	3	06	18	18	018
6. FiO2	*.**	0.21	6. Highest FIO2 on day	0.25	0.21	0.28	0.25		0.21
OR			OR						
7. Supplemental O2 by nasal cannula?			7. Supplemental O2 by nasal cannula?						
8. If FiO2 = .21 (#6), by nasal cannula.		N	8. If FiO2 = .21 (#6), by nasal cannula, CPAP or vent?		Y				N

If in section 'A', snapshot @36 weeks, questions 1-4 are answered NO and either question 6 FiO2 > 0.21 or questions 7 or 8 are answered YES, complete section C :

C. Physiologic Evaluation

1. Is the infant eligible for the physiologic evaluation?

IF YES to question C.1

a. Was the evaluation performed?

b. Date of evaluation

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field

d. If on nasal cannula at time of challenge, record flow rate

e. Did the patient pass the evaluation?

IF NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason:

If 9, explain

```
1= Increased FIO2                                  4= Parent/Physicial Refusal
2= Increased respiratory support (cpap or vent)    6= Weaned to room air on/before day of evaluation
3= Instability (including Surgery/Sepsis)          9= Other-explain
```

Form Completion Date: 05/04/2009

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From: Zaterka-Baxter, Kristin
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, September 28, 2009 9:54:42 AM

Would you like me to call Kim Fisher about these.
Thanks,
Kris

From: Gantz, Marie
Sent: Monday, September 28, 2009 9:52 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT

Yes, however there is a chance that Duke did resolve them but did not send us the query document to tell us how the queries were resolved. I am looking into BPD query resolution today and will let you know what I find.

Marie

Marie Gantz, Ph.D
Research Statistician
RTI International
mgantz@rti.org
919-541-6256

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 28, 2009 9:14 AM
To: Gantz, Marie
Subject: FW: SUPPORT

Marie
Are these the ones that haven't been answered yet?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:53 PM
To: Ronald N Goldberg; Rickl F Goldstein; Michael Cotten; gloria.siaw@duke.edu
Cc: 'Gantz, Marie'
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.
19	[redacted]	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.

CENTER	NETWORK	FU_message
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates
Date: Monday, September 28, 2009 8:55:45 AM

Yes, we have the call today.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 28, 2009 7:51 AM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates

Can we discuss later this am??

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 25, 2009 6:56 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates

Maybe we should go ahead with identification of the group of experts to adjudicate the ROP outcomes as the data will be limited in a substantial proportion of babies.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 25, 2009 3:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin

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Subject: SUPPORT missing data updates

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
2) A few new BPD missing data reminders have been generated for Duke based on recent edits to their data. Kris also has a list of those cases so that they can be addressed at the site visit on Tuesday.
3) We are missing ROP outcomes on 112 infants. Three of those were withdrawn from the study so we probably have all the data we can get on them. There are 2 cases where the infants had vessels in zone 1 at the last exam, 55 cases with vessels in zone 2 at the last exam, and 52 cases where there were vessels in zone 3 at the last exam but not at two consecutive exams (see attached report for details).

My next steps will be to check on the resolution of the BPD and other cross-form queries. Have a good weekend.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; Gantz, Marie
Cc: StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Cunningham, Meg
Subject: RE: SUPPORT Call
Date: Monday, September 28, 2009 8:54:36 AM

Reminder for today's call at **2:00** P.M EST

From: Webb, Robin E.
Sent: Friday, September 11, 2009 12:29 PM
To: higginsr@mail.nih.gov; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik
Cc: StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Webb, Robin E.; Cunningham, Meg; Zaterka-Baxter, Kristin
Subject: SUPPORT Call

The call to discuss SUPPORT has been scheduled for:

Monday 9/28
2:00pm ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Evans, Patricia W"
Cc: "Kathleen A Kennedy"; "Gantz, Marie"
Subject: RE: SUPPORT!!!!
Date: Monday, September 28, 2009 8:42:00 AM

The acute outcomes (death, ROP and BPD) are urgently needed. The FU database will remain open until the last FU window closes (late 2010), but try to get the children in soon.

Hope this helps.

Rose

-----Original Message-----
From: Evans, Patricia W [mailto:Patricia.W.Evans@uth.tmc.edu]
Sent: Friday, September 25, 2009 5:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT!!!!

When is your deadline. We're having trouble finding this baby and if we don't think we have have a chance of finding the family before the deadline we'll have to declare lost to follow-up.

Thank you,

Patricia Wilder Evans, MD
Assistant Professor, Department of Pediatrics
Medical Director, High-Risk Infant Clinic
6431 Fannin St, MSB 3.218
713-500-5311 office
713-500-5794 fax
Patricia.W.Evans@uth.tmc.edu<mailto:Patricia.W.Evans@uth.tmc.edu>

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 4:01 PM
To: Kennedy, Kathleen A; Tyson, Jon E; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Gantz, Marie'
Subject: SUPPORT!!!!

Hi,
We are missing a few SUPPORT Primary outcomes. Please get these entered ASAP as we want to lock the database.

Thanks for all the effort!!
Rose
CENTER

NETWORK

ROP_message

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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CENTER

NETWORK

FU_message

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Michael Cotten"; "Gloria Siaw"; Ronald N Goldberg; "Gantz, Marie"
Subject: Re: SUPPORT!!!!
Date: Saturday, September 26, 2009 4:20:09 PM

Please see the response in red for each query listed. I will follow up with those items not resolved.

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

09/25/2009 05:03 PM

To Ronald N Goldberg <goldb008@mc.duke.edu>, "'Michael Cotten'" <cotte010@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "'Gloria Siaw'" <gloria.siaw@duke.edu>
cc "'Gantz, Marie'" <mgantz@rti.org>
Subject SUPPORT!!!!

Hi,
We are missing a few SUPPORT Primary outcomes. Please get these entered ASAP as we want to lock the database.

Thanks for all the effort!!
Rose

CENTER NETWORK ROP_message

19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status. Subject was LTF at 55 wks and then ROP finalized at 18 mth visit - database updated to reflect these changes
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Subject in foster care and foster mom terminal - we got social worker to sign release for records and we are suppose to have them by Monday - will update database asap
		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. 55 wks is reported in

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19	(b) (6)	database and subject has not come for 18 month visit - we are checking with Duke eye for follow up of ROP- will update asap
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Checking with Duke eye for follow info for 55 week status - will enter asap
19	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders. Subject was reported "4" on (b) (6) both 55 wks status and 18 month status reported in database

CENTER NETWORK BPD_message

19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing. Subject tx (b)(6) 1 and 36 week (b) (6) - database was corrected with this info
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing. Subject tx (b) (6) database was corrected with this info
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing. Subject tx (b) (6) 36 wk (b) (6) database corrected with this info

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Rich, Wade; Wallace, Dennis
Subject: RE: SUPPORT missing data updates
Date: Friday, September 25, 2009 8:29:37 PM

Hi Rose
Mostly we are using survival without NDI and survival without BPD rates for infants of 23 to 28 weeks. I would assume that we would have used that last complete years for NDI. As for the years I think that Kris can tell you that- probably 2006-8.
We are using US rates and have cross referenced with VON. For the death etc and BPD they are close.
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 4:41 PM
To: Finer, Neil
Cc: 'kzaterka@rti.org'; 'dwallace@rti.org'; Rich, Wade
Subject: Re: SUPPORT missing data updates

If unpublished, we need SC permission. Also, PRESOX is an international study, so are US rates ok??
I will send a reqiest to the SC- what years of GDB data and specific rates of all ROP + surgical ROP??
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>; Wallace, Dennis <dwallace@rti.org>; Rich, Wade <wrich@ucsd.edu>
Sent: Fri Sep 25 18:18:41 2009
Subject: Re: SUPPORT missing data updates

Hi Rose
We have used the GDB information via RTI to calculate some sample sizes for our proposed PRESOX Study.
I am not sure whether we would be considered as having permission to use this data for this purpose.
We have acknowledged the source of the data as being from the NRN GDB. I would like to ask whether we need permission and if so, whether you would be so good as to ask the Steering Committee for this.
We are not using any forms from the Network or SUPPORT for this proposed trial
Many thanks for considering this request.
Be well
Neil

On 9/25/09 2:11 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

I just sent out the missing data emails.

Lets hope we get more of the ROP outcomes!!!
Thanks for all your help

Rose

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 25, 2009 4:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
2) A few new BPD missing data reminders have been generated for Duke based on recent edits to their data. Kris also has a list of those cases so that they can be addressed at the site visit on Tuesday.
3) We are missing ROP outcomes on 112 infants. Three of those were withdrawn from the study so we probably have all the data we can get on them. There are 2 cases where the infants had vessels in zone 1 at the last exam, 55 cases with vessels in zone 2 at the last exam, and 52 cases where there were vessels in zone 3 at the last exam but not at two consecutive exams (see attached report for details).

My next steps will be to check on the resolution of the BPD and other cross-form queries. Have a good weekend.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Michael Cotten"; "Gloria Siaw"; Ronald N Goldberg; "Gantz, Marie"
Subject: Re: SUPPORT!!!!
Date: Friday, September 25, 2009 7:26:43 PM

I will work on these this weekend so that they can be completed asap.

Thank you
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b) (6)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

09/25/2009 05:03 PM

To Ronald N Goldberg <goldb008@mc.duke.edu>, "'Michael Cotten'" <cotte010@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "'Gloria Siaw'" <gloria.siaw@duke.edu>
cc "'Gantz, Marie'" <mgantz@rti.org>
Subject SUPPORT!!!!

Hi,
We are missing a few SUPPORT Primary outcomes. Please get these entered ASAP as we want to lock the database.

Thanks for all the effort!!
Rose

CENTER NETWORK ROP_message

19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
		The pt's FU window has closed and final ROP status has not been reported. If

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19	(b) (6)	final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.

CENTER NETWORK BPD_message

19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.

Rosemary D. Higgins, MD
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From: Finer, Neil
To: Wally Carlo; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Abhik Das; Rich, Wade; Zaterka-Baxter, Kristin
Subject: Re: SUPPORT missing data updates
Date: Friday, September 25, 2009 7:09:55 PM

I think that Dale is moving in this direction
I am OK to push on this
Neil

On 9/25/09 3:56 PM, "Wally Carlo" <wcarlo@peds.uab.edu> wrote:

Maybe we should go ahead with identification of the group of experts to adjudicate the ROP outcomes as the data will be limited in a substantial proportion of babies.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 25, 2009 3:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
2) A few new BPD missing data reminders have been generated for Duke based on recent edits to their data. Kris also has a list of those cases so that they can be addressed at the site visit on Tuesday.
3) We are missing ROP outcomes on 112 infants. Three of those were withdrawn from the study so we probably have all the data we can get on them. There are 2 cases where the infants had vessels in zone 1 at the last exam, 55 cases with vessels in zone 2 at the last exam, and 52 cases where there were vessels in zone 3 at the last exam but not at two consecutive exams (see attached report for details).

My next steps will be to check on the resolution of the BPD and other cross-form queries. Have a good weekend.

Thanks,
Marie

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Marie Gantz, Ph.D.
Research Statistician
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828-254-6255

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: Re: SUPPORT missing data updates
Date: Friday, September 25, 2009 6:19:31 PM

Hi Rose
Once we have the final data for BPD we will need Marie to rerun all the stats.
Regards
Neil

On 9/25/09 2:11 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

I just sent out the missing data emails.

Lets hope we get more of the ROP outcomes!!!
Thanks for all your help

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 25, 2009 4:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
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My next steps will be to check on the resolution of the BPD and other cross-form queries. Have a good weekend.

Thanks,
Marie

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Higgins, Rosemary (NIH/NICHD) [E]

From: Bridge, Renee <rbridge@ucsd.edu>
Sent: Friday, September 25, 2009 6:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT!!!

Have changed (b) (6) and (b) (6) to "missing" as requested. Patient (b) (6) does not have the forms NF05 and 09 as the infant was in the hospital for the first visit and no-showed for the next. We have not lost them to follow- up ,but do not have info at this time. Please advise if anything else should be done right away. Renee

---

From: Rich, Wade
Sent: Friday, September 25, 2009 2:30 PM
To: Bridge, Renee
Subject: FW: SUPPORT!!!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 2:04 PM
To: Finer, Neil; Vaucher, Yvonne; Rich, Wade
Cc: 'Gantz, Marie'
Subject: SUPPORT!!!

Hi,
We are missing a few SUPPORT Primary outcomes. Please get these entered ASAP as we want to lock the database.

Thanks for all the effort!!
Rose

CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.

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CENTER

NETWORK

FU_message

22

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates
Date: Friday, September 25, 2009 5:34:08 PM

THANKS!!!

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 25, 2009 4:12 PM
To: 'Gantz, Marie'
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT missing data updates

I just sent out the missing data emails.

Lets hope we get more of the ROP outcomes!!!
Thanks for all your help

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 25, 2009 4:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
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My next steps will be to check on the resolution of the BPD and other cross-form queries. Have a good

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weekend.

Thanks,
Marie

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Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Rich, Wade; Wally Carlo, M.D.; Zaterka-Baxter, Kristin
Subject: SUPPORT missing data updates
Date: Friday, September 25, 2009 4:52:13 PM
Attachments: Infants with missing outcomes 09-24-09.xls
SUPPORT infants with missing ROP 09-24-09.rtf

Attached are is the list of SUPPORT infants who are currently missing outcome data. A few things to note:

1) Our N is now 1317 instead of 1316 because Duke just entered forms for an infant whose parent had consented for SUPPORT but who did not consent to GDB until the 18 month FU visit.
2) A few new BPD missing data reminders have been generated for Duke based on recent edits to their data. Kris also has a list of those cases so that they can be addressed at the site visit on Tuesday.
3) We are missing ROP outcomes on 112 infants. Three of those were withdrawn from the study so we probably have all the data we can get on them. There are 2 cases where the infants had vessels in zone 1 at the last exam, 55 cases with vessels in zone 2 at the last exam, and 52 cases where there were vessels in zone 3 at the last exam but not at two consecutive exams (see attached report for details).

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Thanks,
Marie

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Missing_BPD

CENTER	NETWORK	BPD_message
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19		Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.
19		Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing.

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Reasons ROP is missing

The FREQ Procedure

Reason for no ROP classification				
noropreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
-1 Infant withdrawn	3	2.68	3	2.68
2 Lowest zone of any vessels is I at last exam	2	1.79	5	4.46
3 Lowest zone of any vessels is II at last exam	55	49.11	60	53.57
4 Lowest zone of any vessels is II for one exam	52	46.43	112	100.00

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=2=Lowest zone of any vessels is I at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels, previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels, previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
1	33	3	P	1	P	199	Y	N	3=Closed
2	47	1	2	1	2	245	Y	N	3=Closed

Reason for no ROP classification=3=Lowest zone of any vessels is II at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels, previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels, previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
3	38	2	2	2	2	55			1=Not open yet
4	41	2	2	2	2	56			1=Not open yet
5	40	2	2	2	2	58			1=Not open yet
6	36	2	2	2	2	60	Y		1=Not open yet
7	38	2	2	2	2	62	Y		1=Not open yet
8	38	2	2	2	2	63			1=Not open yet
9	33	2	1	2	1	65			1=Not open yet
10	37	2	2	2	2	65			1=Not open yet
11	35	2	2	2	2	68			1=Not open yet
12	49	2	2	2	2	69		N	.
13	37	2	2	2	2	74	Y		1=Not open yet
14	33	2	.	2	.	75			1=Not open yet
15	39	2	2	2	2	77	Y		1=Not open yet
16	41	2	2	2	2	81	Y		1=Not open yet
17	42	3	2	2	2	82			1=Not open yet
18	33	2	2	2	2	83	Y		1=Not open yet
19	35	2	2	2	2	85	Y		1=Not open yet
20	37	2	2	2	2	89			1=Not open yet
21	35	2	2	2	2	90			1=Not open yet
22	34	2	2	2	2	93	Y		1=Not open yet
23	38	2	2	2	2	94	Y		1=Not open yet
24	36	2	2	2	2	101			1=Not open yet
25	38	2	1	2	1	106	Y		1=Not open yet
26	49	2	3	2	3	111	Y		1=Not open yet
27	43	2	2	2	2	113			1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels, previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels, previous exam	Current estimated PMA	Acute ROP status as of FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
28	50	2	2	2	2	113	Y		1=Not open yet
29	44	2	2	2	2	113	Y		1=Not open yet
30	42	2	2	2	2	113		N	1=Not open yet
31	38	2	2	2	2	116	Y		1=Not open yet
32	36	2	2	2	2	117			1=Not open yet
33	38	2	2	2	2	123			2=Open now
34	36	2	2	2	2	125	Y		2=Open now
35	32	2	1	2	1	127		N	2=Open now
36	38	2	2	2	2	129	Y		2=Open now
37	36	2	2	2	2	130	Y		2=Open now
38	65	2	2	2	2	130	Y	N	2=Open now
39	41	2	2	2	2	136			2=Open now
40	77	2	2	2	2	138		N	3=Closed
41	34	2	2	2	2	139	Y	N	3=Closed
42	46	2	2	2	2	142		N	3=Closed
43	33	2	.	2	.	147	Y	N	3=Closed
44	44	2	2	2	2	149	Y	N	3=Closed
45	71	2	2	2	2	153		N	3=Closed
46	85	2	2	2	2	156	Y	N	3=Closed
47	55	9	2	9	2	159	Y	N	3=Closed
48	39	2	2	2	2	159			3=Closed
49	44	2	2	2	2	195	Y	N	3=Closed
50	43	2	2	2	2	206			3=Closed
51	37	2	2	2	2	208	Y	N	3=Closed
52	94	2	2	2	2	230	Y	N	3=Closed
53	34	2	2	2	2	230	Y	N	3=Closed
54	78	2	2	2	2	244	Y	N	3=Closed
55	35	2	2	2	2	251	Y	N	3=Closed
56	64	2	2	2	2	253	Y	N	3=Closed
57	36	2	2	2	2	253		N	3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=4=Lowest zone of any vessels is III for one exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status last to FU at 55 weeks PMA	Final ROP status documented at FU	FU window
58	39	3	1	3	2	57		N	.
59	50	3	2	3	2	68			1=Not open yet
60	38	3	2	3	2	71	Y		1=Not open yet
61	34	3	2	3	2	72	Y		1=Not open yet
62	36	3	.	3	.	73			1=Not open yet
63	38	3	2	3	2	74	Y		1=Not open yet
64	39	3	2	3	2	78	Y		1=Not open yet
65	40	3	2	3	2	82	Y		1=Not open yet
66	36	3	2	3	2	83	Y		1=Not open yet
67	37	3	2	3	2	85	Y		1=Not open yet
68	35	3	2	3	2	87			1=Not open yet
69	41	3	2	3	2	93	Y		1=Not open yet
70	35	3	2	3	2	95	Y		1=Not open yet
71	41	3	2	3	2	98	Y		1=Not open yet
72	40	3	2	3	2	98	Y		1=Not open yet
73	36	3	2	3	2	101	Y		1=Not open yet
74	37	3	2	3	2	102	Y		1=Not open yet
75	39	3	2	3	2	103	Y		1=Not open yet
76	38	3	2	3	2	104	Y		1=Not open yet
77	35	3	2	3	2	105	Y		1=Not open yet
78	38	3	2	3	2	106			1=Not open yet
79	39	3	2	3	2	109	Y		1=Not open yet
80	33	3	2	3	2	114			1=Not open yet
81	40	3	2	3	2	114	Y		1=Not open yet
82	34	3	2	3	2	115	Y		1=Not open yet
83	36	3	2	3	2	116			1=Not open yet
84	39	3	2	3	2	116			1=Not open yet
85	41	3	2	3	2	118	Y	N	2=Open now
86	34	3	2	3	2	119	Y	N	2=Open now
87	36	3	2	3	2	130	Y		2=Open now
88	48	3	2	3	2	131			2=Open now
89	44	3	2	3	2	140	Y		3=Closed
90	44	3	2	3	2	144			3=Closed
91	38	3	2	3	2	155			3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels* previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels* previous exam	Current estimated PMA	Acute ROP Status lost to FU at 55 weeks PMA	Final ROP status obtained	FU window
92	37	3	2	3	2	159	Y	N	3=Closed
93	39	3	2	3	2	159			3=Closed
94	46	3	2	3	2	171	Y	N	3=Closed
95	38	3	2	3	2	183	Y	N	3=Closed
96	44	3	2	3	2	226	Y		3=Closed
97	37	3	2	3	2	232	Y	N	3=Closed
98	55	3	2	3	2	233	Y		3=Closed
99	34	3	2	3	3	235		N	3=Closed
100	32	3	.	3	.	237	Y	N	3=Closed
101	33	3	P	3	P	239	Y	N	3=Closed
102	36	3	2	3	2	247	Y	N	3=Closed
103	39	3	2	3	2	247	Y	N	3=Closed
104	33	3	P	3	P	249	Y	N	3=Closed
105	34	3	2	3	2	251	Y	N	3=Closed
106	86	3	2	3	2	251	Y	N	3=Closed
107	39	3	2	3	2	252	Y	N	3=Closed
108	88	3	2	3	2	257	Y	N	3=Closed
109	37	3	2	3	2	261	Y	N	3=Closed

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support cross-checks
Date: Friday, September 25, 2009 4:27:14 PM
Attachments: SUPPORT cross-form queries Center 19 04SEP09.rtf

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (10:42) does not match SUPP03 delivery time (10:24).	NG03e death date/time (b) (6)) is before NG02 birth date/time (b) (6)	SUPP03 surfactant date/time (b) (6)) is before NG02 birth date/time (b) (6)		Time was corrected and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)				Status corrected to match and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant was outborn per NG02 but was enrolled in SUPPORT.				Error infant not outborn

Center ID number=19 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is death but status date (Q A.2.) (b) (6) is different from death date (Q O.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (5=Death) but dates are different (b) (6)) vs (b) (6)			Dates corrected to reflect (b) (6)

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (20:00) does not match SUPP03 delivery time (20:05).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)) vs (b) (6)			Pt transferred (b) (6) prior to 36 week – not available for 02 challenge, info entered and transmitted

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG05 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q D.1.) (b) (6)				Status corrected and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)				Time corrected and transmitted

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				Info placed on wrong line – corrected and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 14 but PVL is not recorded on SUPP09.				Info corrected and transmitted

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on SUPP09.			Info corrected and transmitted

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 11 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 11 but severe IVH is not recorded on NG03.			NG03 corrected and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)				Date corrected to (b) (6) transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 9 but severe IVH is not recorded on NG03.				NG03 corrected and transmitted

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was >120 days ago but SUPP09 has not been completed.				Pt discharged on (b) (6) and 120 days is (b) (6)

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			Still working on this one

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution Center notes
Birth date was >120 days ago but SUPP09 has not been completed.				Pt discharged on (b) (6) and 120 days on (b) (6)

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution Center notes
Birth date was >120 days ago but SUPP09 has not been completed.				Pt discharged on (b) (6) and 120 days on (b) (6)

Center ID number=19 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution Center notes
Birth date was >120 days ago but SUPP09 has not been completed.	Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.			Currently working to complete all this info but will transmit what is currently entered

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Huitema, Carolyn Petrie
Subject: FW: Support IDs
Date: Friday, September 25, 2009 3:58:28 PM
Attachments: SUPPORT data for Duke visit 09-29-09.doc

These are the primary outcomes on spreadsheet you requested so you can review prior to the Duke visit
Thanks,
Kris

From: Gantz, Marie
Sent: Friday, September 25, 2009 3:41 PM
To: Zaterka-Baxter, Kristin
Subject: RE: Support IDs

Hi – see if the attached document is OK. I have BPD and ROP data on separate pages – if that's a problem I'll try to figure out some other format. I've included a note after the BPD data to point out cases that used to have the NG07 snapshot data but now do not. Also, there is a note for the infant who used to have an NG03 but now does not. Let me know if you need anything else!

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
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828-254-6255

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SUPPORT Data for Duke Visit 09/29/09 (BPD Data)

Network number	Date of BPD	Status at 36 wks PMA	BPD (physician definition)	BPD (phys def) day 1 O2	Reason for BPD (phys def) determination	BPD (supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	RTI note
(b) (6)		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Hospitalized	Y	PHY02RA/NG07v3C	Challenge result	Y	NG07	On supplemental O2 @36wks	
		Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	NG07 36wk snapshot has been deleted
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
(b) (6)		Transferred	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @status	NG07 36wk snapshot has been deleted
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	

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SUPPORT Data for Duke Visit 09/29/09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (physiologic definition)	BPD physiologic data source	RA? or to BPD (physiologic) determination	BPD (supplemental O2)	BPD (O2) data source	Reason for RA (O2) determination	RTI note
(b) (6)		Transferred	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	NG07 36wk snapshot has been deleted
		Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	N	NG07	RA @36wks	
		Discharged on day of 36 wks PMA	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		.	.	.	.	.	.	.	NG03 & NG07 36wk snapshot have been deleted
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Discharged	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Discharged	N	SUPP11	RA by NC flow<=.5 lpm @status	N	NG07	RA @status	
		Discharged	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
(b) (6)		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	Y	PHY01/NG07v3C	On vent/CPAP @36wks	Y	NG07	On supplemental O2 @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Transferred	Y	SUPP11	On vent/CPAP @status	N	NG07	RA @status	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	

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SUPPORT Data for Duke Visit 09/29/09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (phys def. definition)	BPD (phys. def. data source)	Reason for BPD (phys. def. determination	BPD (Supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	RT note
(b) (6)		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	.	.	.	.	.	.	NG07 36wk snapshot has been deleted
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	NG07 36wk snapshot has been deleted
		Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
		Transferred	Y	SUPP11	On vent/CPAP @status	N	NG07	RA @status	
(b) (6)		Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	
		Transferred	Y	NG07	On supplemental O2 @status	Y	NG07	On supplemental O2 @status	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	NG07 36wk snapshot has been deleted
		Hospitalized	N	PHY01/NG07v3C	Not challenged reason (weaned to RA)	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	Y	NG07	On vent/CPAP @36wks	N	NG07	RA @36wks	
		Death	.	.	Died by 36 weeks	.	.	Died by 36 weeks	

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SUPPORT Data for Duke Visit 09/29/09 (BPD Data)

Network number	Date of Birth	Status at 36 weeks PMA	BPD (physiologic definition)	BPD (physician data source)	Reason for BPD (physician determination)	BPD (Supplemental O2)	BPD (O2) data source	Reason for BPD (O2) determination	RTI note
(b) (6)		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Hospitalized	Y	NG07	On vent/CPAP @36wks	N	NG07	RA @36wks	
		Hospitalized	N	NG07	RA (not by NC/CPAP/vent) @36wks	N	NG07	RA @36wks	
		Transferred	N	NG07	RA (not by NC/CPAP/vent) @status	N	NG07	RA @status	

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SUPPORT Data for Duke Visit 09/29/09 (ROP Data)

Patient number	Final status	Left eye ROP stage III	Left eye ROP	Left eye ROP location	Right eye ROP stage III	Right eye ROP	Right eye ROP location	PI initials
(b) (6)	Death	.	.	.	.	.	.	
	Discharged	N	.	.	N	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	N	.	.	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	Y	ROP surgery	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
(b) (6)	Death	.	.	.	.	.	.	
	Discharged	Y	Y	ROP surgery	Y	Y	ROP surgery	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	.	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	Y	ROP stage 4 or 5	

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SUPPORT Data for Duke Visit 09/29/09 (ROP Data)

Network number	Reason for exit	Left eye ROP in 1st	Left eye ROP	Left eye ROP reason	Right eye ROP in 1st	Right eye ROP	Right eye ROP reason	PI initials
(b) (6)	Discharged	N	.	.	N	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	Y	ROP surgery	Y	Y	ROP surgery	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Death	.	.	.	.	.	.	
	Discharged	N	.	.	N	.	.	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
(b) (6)	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	N	Lowest zone = mature	Y	N	Lowest zone = mature	
	Discharged	Y	Y	ROP surgery	Y	Y	ROP surgery	
	Death	.	.	.	.	.	.	
	Discharged	Y	N	Lowest zone = III for consecutive exams	Y	N	Lowest zone = III for consecutive exams	
	Discharged	N	.	.	N	.	.	
	Discharged	Y	Y	ROP surgery	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	Threshold (Type I) ROP	Y	Y	Threshold (Type I) ROP	
	Discharged	Y	Y	ROP surgery	Y	Y	ROP surgery	
	Discharged	N	.	.	N	.	.	
	Discharged	N	.	.	N	.	.	

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Cunningham, Meg
Subject: FW: SUPPORT Call
Date: Thursday, September 24, 2009 11:56:32 AM

Hi Rose,

Does Marie need to be on this call? Anyone else?
Thanks,
Kris

From: Webb, Robin E.
Sent: Friday, September 11, 2009 12:29 PM
To: higginsr@mail.nih.gov; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik
Cc: StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Webb, Robin E.; Cunningham, Meg; Zaterka-Baxter, Kristin
Subject: SUPPORT Call

The call to discuss SUPPORT has been scheduled for:

Monday 9/28
2:00pm ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6) #

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From: Wally Carlo, M.D.
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper
Date: Tuesday, September 22, 2009 12:29:13 PM

GREAT!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, September 22, 2009 11:28 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

I have not looked at that since I've been back, but I will send you an update this week after the data upload.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 22, 2009 12:26 PM
To: Gantz, Marie; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Ho are we doing on ROP??

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, September 22, 2009 12:25 PM
To: Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Once we have the outstanding queries resolved we can probably lock the dataset for the BPD, death and

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secondary outcomes. I will check to see where we stand after our data are updated with today's transmission from the centers.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, September 21, 2009 5:56 PM
To: Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi ALL:

Maybe we should discuss on a call which numbers to use for Figure 1.

Marie:

Thanks a lot for your comments.

When do you estimate we could think of data closure for all but the ROP outcomes?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, September 21, 2009 3:43 PM
To: Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi all,

Thanks for your patience while I was away. I have made few edits and comments to the latest version of Wally's paper. Wally, you had mentioned that you were missing some outcomes (like IVH/death) and I believe those were included in tables I sent on Sept. 3 (T2S Major Outcomes - PRELIMINARY 03SEP09.doc) – let me know if you need me to resend them.

Regarding the earlier question about the numbers in figure 1 differing from the monthly report, in the monthly report "*Eligible GDB patients are those keyed in the NG02 (inborn and GA*

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of 24 0/6 & 27 6/7) with a birth date after the first Support patient keyed for sites at each Center and not born on or between dates of Support study suspension 11/23/2005 and 2/5/2006" while the 3546 in figure 1 are those infants who were entered on the SUPP01 screening log. I'm not sure what to do about the difference unless we add them to the number who were "eligible but consent not sought." We should also be clear in figure 1 that many more moms were screened than are reflected on the SUPP01, because only those infants who were eventually assigned a GDB number (or who were enrolled in SUPPORT) were entered into the DMS. We could reference Wade's antenatal consent paper for a more accurate estimate of how many moms were screened.

FYI, while I was gone, queries went out to the centers regarding data that differed across GDB and SUPPORT forms and that will impact the secondary outcomes (including things like IVH) to some (hopefully small) degree. We have heard back from 10 centers so far, and I will review the results of the queries as we get responses to make sure all the necessary data are cleaned. I will also re-review the BPD outcome data to see if those queries have been completely cleared up yet and I will remind centers of any outstanding queries.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 18, 2009 9:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

Hi Wally
I have made a few changes
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 18, 2009 1:29 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper

Dear Neil, Rose, Abhik, and Marie:

I have made several changes including:
1. Making Neil's suggestions
2. Improved Figure 2
3. Included Figure 1
4. Multiple minor changes.

I have made changes in all the numbers of the results as Abhik said they are still not final.

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Enclosed is a clean draft so you can see my comments. I think we need to consider adding the ROP data if it is final before the paper is ready for submission.

I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oxygen saturation targeting paper
Date: Monday, September 21, 2009 7:13:25 PM

Ok. You are right. Next week is best as scheduled.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 21, 2009 5:54 PM
To: Wally Carlo, M.D.
Subject: Re: Oxygen saturation targeting paper

The SC call is tomorrow- the SUPPORT call is monday -we cold do tomorrow, but I need to make sure Neil is available
Rosemary D. Higgins, MD
Program Scientist

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 21 18:43:16 2009
Subject: RE: Oxygen saturation targeting paper

Rose:

GREAT! Maybe we can do it at the end as we do not need the whole SC. What do you think?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

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Sent: Monday, September 21, 2009 5:06 PM
To: Wally Carlo, M.D.
Subject: Re: Oxygen saturation targeting paper

Wally
We have a call scheduled for 9/28 at 2 pm. Can we discuss at this time?
If I try to set something up this week, we will likely lose folks. Let me know

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Gantz, Marie <mgantz@rti.org>; Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>
Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Mon Sep 21 17:55:58 2009
Subject: RE: Oxygen saturation targeting paper

Hi ALL:

Maybe we should discuss on a call which numbers to use for Figure 1.

Marie:

Thanks a lot for your comments.

When do you estimate we could think of data closure for all but the ROP outcomes?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Birmingham, AL 35233-7335
Phone: 205 934 4680
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Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, September 21, 2009 3:43 PM
To: Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

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Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 18, 2009 9:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

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Be well
Neil

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Sent: Friday, September 18, 2009 1:29 PM
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Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper

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3. Included Figure 1
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I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
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University of Alabama at Birmingham
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Phone: 205 934 4680
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Cell: 205 266 (b) (6)

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From: Gantz, Marie
To: Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper
Date: Monday, September 21, 2009 4:43:12 PM
Attachments: Oxygen Saturation Targeting 9 18 09Rev NF MG.doc

Hi all,

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Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 18, 2009 9:52 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper

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Sent: Friday, September 18, 2009 1:29 PM

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Thanks
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9/18/09
4.0

The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

Waldemar A. Carlo, M.D.
University of Alabama at Birmingham
525 New Hillman Building
619 South 20th Street
Birmingham, AL 35233

Phone: (205) 934 4680
Fax: (205) 934 3100
Email: wcarlo@peds.uab.edu

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9/18/09
4.0

Word count:

Abstract: 93

Manuscript: 1921

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to also increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80mmHg.[14]

The recent introduction of pulse oximeters into the neonatal intensive care units, have allowed clinicians to utilize oxygen saturations to target oxygenation in premature infants. A survey study of 144 neonatal intensive care units conducted in 2001, revealed that the average lower limit of target oxygen saturations was 90% and the upper limit was 96%.[5] In recent years, the use of high saturation targets has been associated with the increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%) or $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%).[5] Recent studies suggest that oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy. In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe

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retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, in these studies, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting and ventilation strategy. ~~. testing~~ The oxygen saturation arm tested the effect of a lower oxygen saturation target range (85-89%) ~~as~~ compared to a higher oxygen saturation target range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. ~~The factorial design allowed comparison~~ The ventilation arm tested the effect of ~~of~~ prophylactic/early surfactant versus continuous positive airway pressure~~; thus, controlling for the approach to ventilatory support~~ on bronchopulmonary dysplasia or death at 36 weeks postmenstrual age.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age, without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiple births were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95%. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[20] Participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy. The oxygen saturation values displayed reverted to actual values when less than 845% or greater than 965%. Oxygen saturation targeting with the altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were

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placed back on the assigned study pulse oximetry. Adjustments in supplemental oxygen to target oxygen saturations were performed by the clinicians, not by the research staff.

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge or 120 days postnatal age whichever occurred first. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Outcomes included predefined clinical diagnoses and potential adverse events.

Comment [MG1]: We are also including treatment with Avastin, correct?

Statistical analysis

The primary analysis for the oxygen saturation arm of this factorial trial was a ~~logistic regression~~ generalized estimating equation (GEE) model that used robust Poisson regression to produce adjusted relative risks comparing ~~analysis of~~ the percentages of infants in each group (lower versus higher oxygen saturations) who developed the primary outcome. The model adjusted for stratification by center and gestational age and for the randomization of multiple births to the same treatment. An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll ~~1312~~ 1310 infants for 80% power to detect a 10% difference in outcome

Comment [MG2]: This is what is listed on clinicaltrials.gov

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assuming ~~and~~ a baseline estimated rate of ~~45~~50% of death/threshold retinopathy/surgery. This sample size estimate included ~~. based on~~ an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. The trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted by the data center. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons. An independent data safety and monitoring committee reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock boundaries were used to develop stopping rules for interim safety monitoring.

Comment [MG3]: The final DSMC review will take place on November 4 to review 100% of the BPD/death data and as much of the ROP data as we have at that time.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily stopped by the Data Safety and Monitoring Committee because of concerns regarding compliance with oxygen saturation targets. Separate of analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns. The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The Data Safety and Monitoring Committee masked interim analyses were made available to the investigators after enrollment was completed. There had been a trend for increased mortality in one of the treatment groups that had not reached the stopping boundary. The principal investigator and data

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center staff undertook a safety analysis to evaluate potential adverse outcomes without unblinding the retinopathy outcome data. This manuscript reports the hospital outcomes. Retinopathy and 18-22 month follow up outcomes will be reported later.

Mortality at any time during hospitalization occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed in both gestational age groups used for stratification. Mortality in the first and second weeks after birth was comparable in the two groups (Table 2). Other prespecified major outcomes were comparable between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was some overlap (Figure 2). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation

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was practiced in the 1950s and 1960s. Despite not~~w~~ being based on randomized controlled trials and limited evidence of safety, lower oxygen saturation targeting has become ~~the recommended~~increasingly adopted by units and physicians who are desirous of decreasing significant retinopathy of prematurity. In the current trial, lower oxygen saturation targeting (85-89%) resulted in an increased risk of mortality.

This trial was not prospectively powered for a difference in mortality only between the two oxygen saturation groups and, thus, the results should be viewed with caution. However, this is the largest completed prospective randomized trial to test the effect of lower versus higher oxygen saturation targeting and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trails of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence ~~rather than~~compared to randomized controlled trials. It is interesting and worrisome that the ~~,~~combined risk difference observed in the 1950s ~~except for the trends in the 1950s which had a combined risk difference of~~~~was a~~ was a 4.9% increase in mortality in the oxygen restricted group very similar to our 4% mortality increase in the lower targeted SpO2 group. (Ref 1).

Comment [MG4]: Although death was not the pre-specified primary outcome, the fact that the study was not specifically powered to detect a difference in death rate should not in itself lead us to be cautious about the findings. Recall that the study was powered conservatively for an outcome rate of 50% . It turned out that we also had the power to detect a difference in death rates of 16% vs. 20%.

Restriction of oxygenation in the randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group.

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Mortality in the current trial did not differ by 7 or 14 days. Therefore, the lower target of oxygen saturations rather than the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[1] At the present time, it is important that these trials continue.~~. It is also~~and it will be important that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no.(%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Relative Risk (95% CI)
Death before discharge	130/655 (20)	106/661 (16)	
Death by 7 days	41/655 (6)	38/661 (6)	
Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	
Pneumothorax – no. (%)	48/655 (7)	43/661 (7)	
Any air leaks – no. (%)	50/655 (8)	43/661 (7)	

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Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

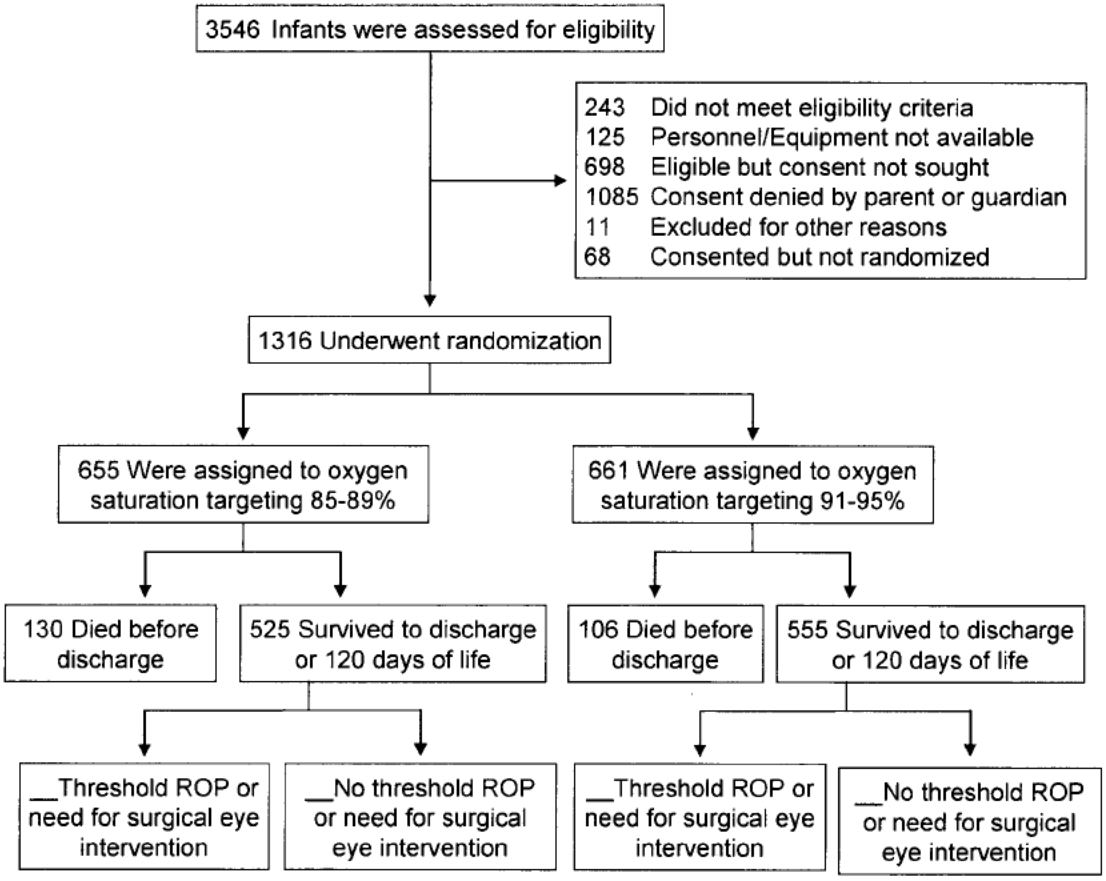

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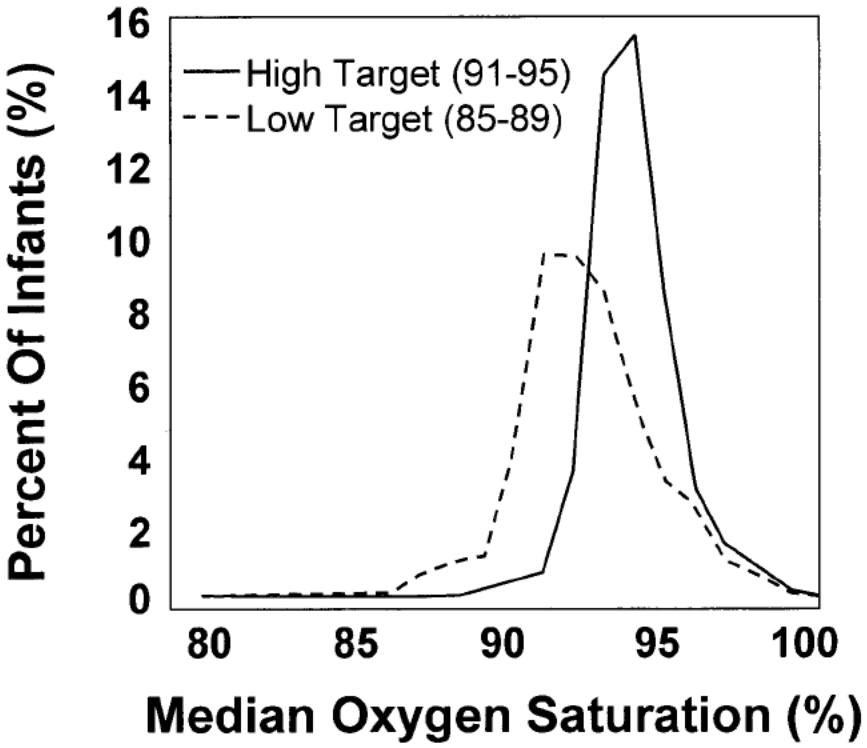
Figure 2



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From: Finer, Neil
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Oxygen saturation targeting paper
Date: Friday, September 18, 2009 9:52:15 PM
Attachments: Oxygen Saturation Targeting 9 18 09Rev NF.doc

Hi Wally
I have made a few changes
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 18, 2009 1:29 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper

Dear Neil, Rose, Abhik, and Marie:

I have made several changes including:
1. Making Neil's suggestions
2. Improved Figure 2
3. Included Figure 1
4. Multiple minor changes.

I have made changes in all the numbers of the results as Abhik said they are still not final.

Enclosed is a clean draft so you can see my comments. I think we need to consider adding the ROP data if it is final before the paper is ready for submission.

I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
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University of Alabama at Birmingham
Director, Division of Neonatology
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The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Word count:

Abstract: 93

Manuscript: 1921

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to also increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80mmHg.[14]

The recent introduction of pulse oximeters into the neonatal intensive care units, have allowed clinicians to utilize oxygen saturations to target oxygenation in premature infants. A survey study of 144 neonatal intensive care units conducted in 2001, revealed that the average lower limit of target oxygen saturations was 90% and the upper limit was 96%.[5] In recent years, the use of high saturation targets has been associated with the increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%) or $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%).[5] Recent studies suggest that oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy. In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe

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retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, in these studies, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting, testing the effect of a lower oxygen saturation range (85-89%) as compared to a higher oxygen saturation range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. The factorial design allowed comparison of prophylactic/early surfactant versus continuous positive airway pressure; thus, controlling for the approach to ventilatory support.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

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Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age, without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiple births were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95%. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[20] Participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy. The oxygen saturation values displayed reverted to actual values when less than 85% or greater than 95%. Oxygen saturation targeting with the altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximetry. Adjustments in supplemental oxygen to target oxygen saturations were performed by the clinicians, not by the research staff.

Assessments

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Research nurses recorded all data using standardized definitions. Data were collected until discharge or 120 days postnatal age whichever occurred first. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Outcomes included predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of this factorial trial was a logistic regression analysis of the percentages of infants in each group (lower versus higher oxygen saturations) who developed the primary outcome. An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1312 infants for 80% power and a baseline estimated rate of 45% of death/threshold retinopathy/surgery, based on an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and on an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. The trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted by the data center. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses did not include adjustment for multiple comparisons.

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An independent data safety and monitoring committee reviewed the primary outcomes, adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily stopped by the Data Safety and Monitoring Committee because of concerns regarding compliance with oxygen saturation targets. Separate of analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns. The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The Data Safety and Monitoring Committee masked interim analyses were made available to the investigators after enrollment was completed. There had been a trend for increased mortality in one of the treatment groups that had not reached the stopping boundary. The principal investigator and data center staff undertook a safety analysis to evaluate potential adverse outcomes without unblinding the retinopathy outcome data. This manuscript reports the hospital outcomes. Retinopathy and 18-22 month follow up outcomes will be reported later.

Mortality at any time during hospitalization occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed in both gestational age groups used for stratification. Mortality in the first and second weeks after birth was comparable in the

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two groups (Table 2). Other prespecified major outcomes were comparable between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was some overlap (Figure 2). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ.

DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite not~~w~~ being based on randomized controlled trials and limited evidence of safety, lower oxygen saturation targeting has become ~~the recommended~~increasingly adopted by units and physicians who are desirous of decreasing significant retinopathy of prematurity. In the current trial, lower oxygen saturation targeting (85-89%) resulted in an increased risk of mortality.

This trial was not prospectively powered for a difference in mortality only between the two oxygen saturation groups and, thus, the results should be viewed with caution. However, this is the largest completed prospective randomized trial to test the effect of lower versus higher oxygen saturation

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targeting and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm infants. The infants in this trial were more immature than those of any previous trails of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction. The previous data on the increased mortality from oxygen restriction were from studies with lower levels of evidence ~~rather than~~compared to randomized controlled trials. It is interesting and worrisome that the ~~,~~combined risk difference observed in the 1950s ~~except for the trends in the~~ 1950s ~~which had a combined risk difference of~~was a was a 4.9% increase in mortality in the oxygen restricted group very similar to our 4% mortality increase in the lower targeted SpO2 group. (Ref 1).

Restriction of oxygenation in the randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group. Mortality in the current trial did not differ by 7 or 14 days. Therefore, the lower target of oxygen saturations rather than the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[1] At the present time, it is important that these trials continue.~~,~~ ~~It is also~~and it will be important that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further

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information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no.(%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Relative Risk (95% CI)
Death before discharge	130/655 (20)	106/661 (16)	
Death by 7 days	41/655 (6)	38/661 (6)	
Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	
Pneumothorax – no. (%)	48/655 (7)	43/661 (7)	
Any air leaks – no. (%)	50/655 (8)	43/661 (7)	

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Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

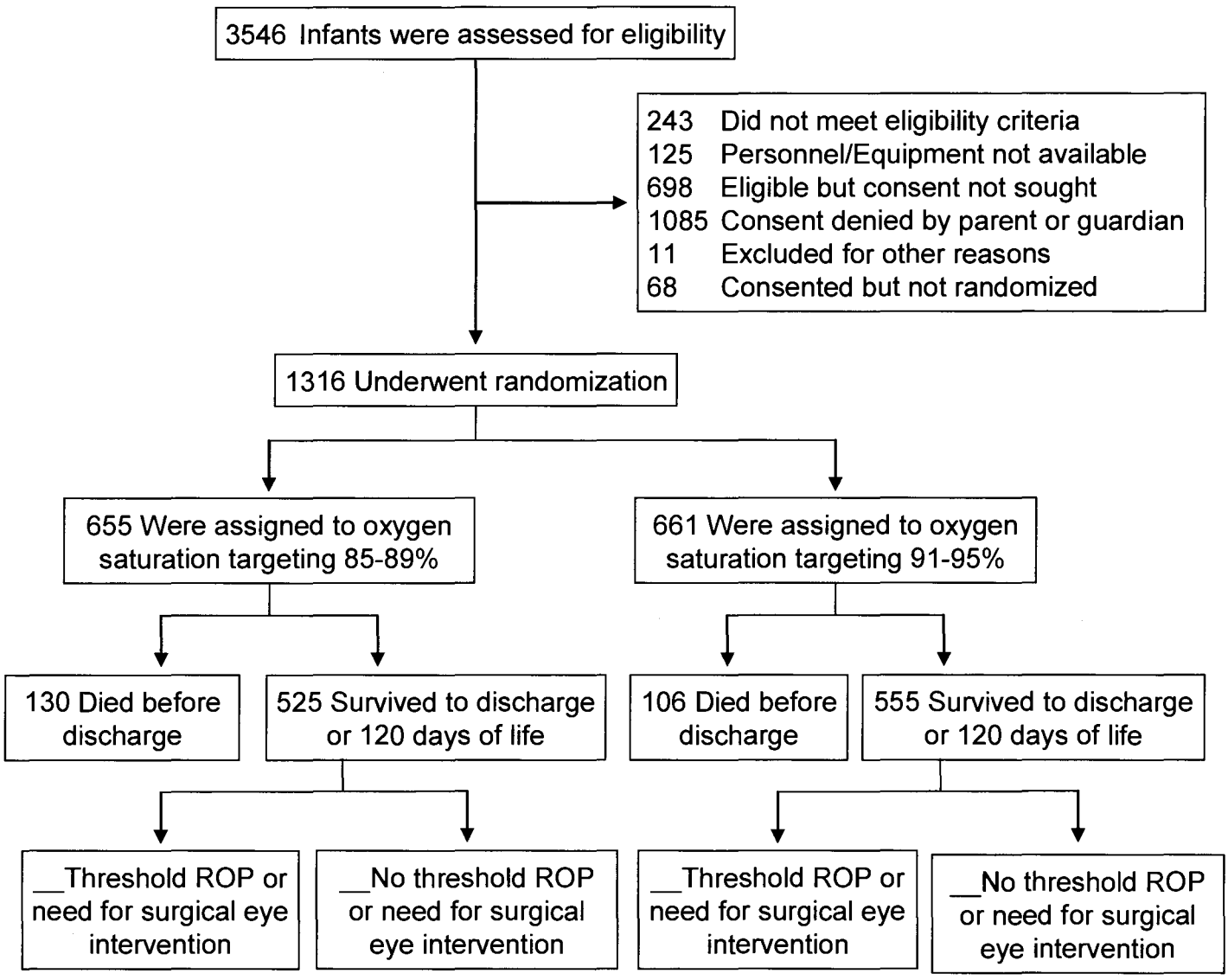

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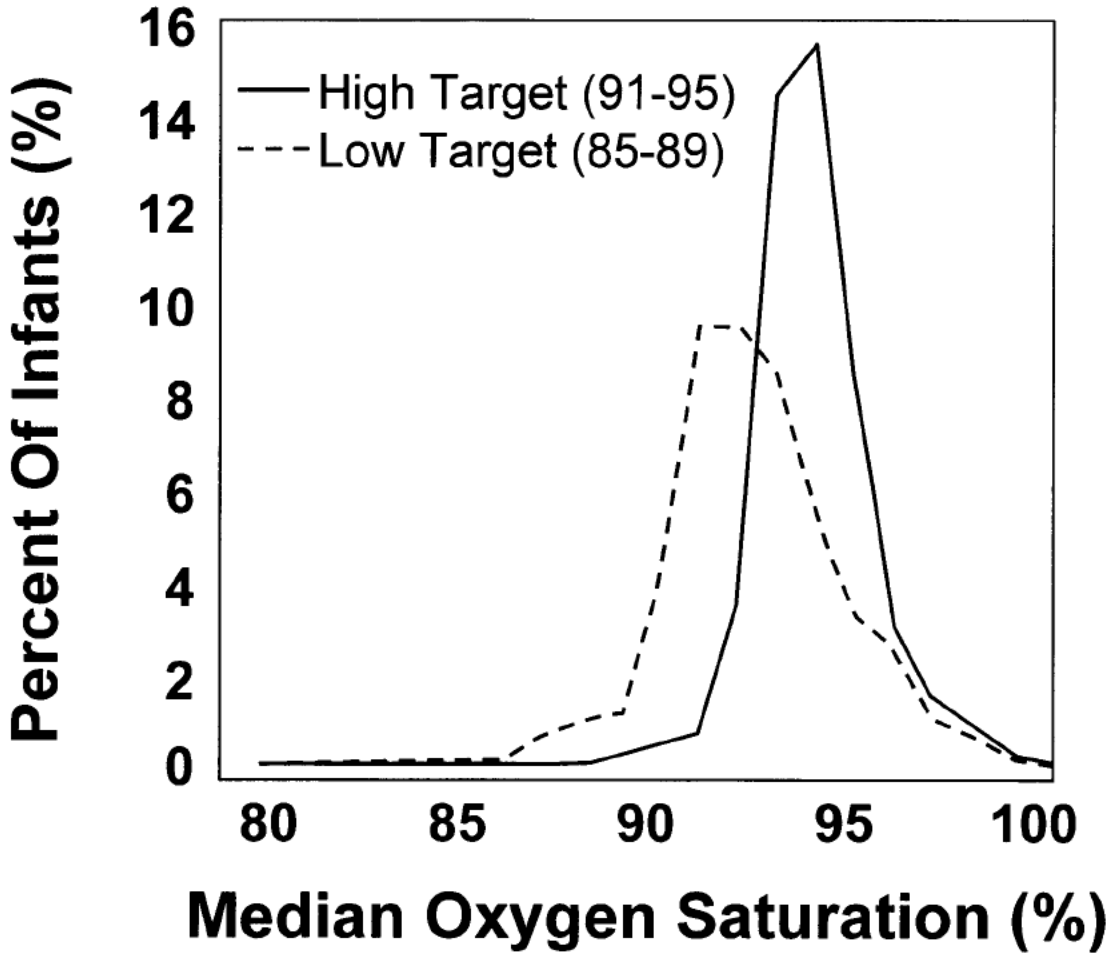
Figure 2



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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: Oxygen saturation targeting paper
Date: Friday, September 18, 2009 4:28:52 PM
Attachments: Oxygen Saturation Targeting.9.18.09.doc

Dear Neil, Rose, Abhik, and Marie:

I have made several changes including:
1. Making Neil's suggestions
2. Improved Figure 2
3. Included Figure 1
4. Multiple minor changes.

I have made changes in all the numbers of the results as Abhik said they are still not final.

Enclosed is a clean draft so you can see my comments. I think we need to consider adding the ROP data if it is final before the paper is ready for submission.

I would appreciate any comments.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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Phone: 205 934 4680
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The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Manuscript: 1921

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Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities in prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, in subsequent years, the practice of restricting oxygen supplementation was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to also increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Although a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association of retinopathy with exposure to arterial oxygen levels $\geq$ 80mmHg.[14]

The recent introduction of pulse oximeters into the neonatal intensive care units, have allowed clinicians to utilize oxygen saturations to target oxygenation in premature infants. A survey study of 144 neonatal intensive care units conducted in 2001, revealed that the average lower limit of target oxygen saturations was 90% and the upper limit was 96%.[5] In recent years, the use of high saturation targets has been associated with the increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%) or $\geq$ 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%).[5] Recent studies suggest that oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy. In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe

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retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, in these studies, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels do so without an increase in serious adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting, testing the effect of a lower oxygen saturation range (85-89%) as compared to a higher oxygen saturation range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. The factorial design allowed comparison of prophylactic/early surfactant versus continuous positive airway pressure; thus, controlling for the approach to ventilatory support.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

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Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age, without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiple births were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by center and by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks). Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95%. Masking was maintained using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[20] Participants were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy. The oxygen saturation values displayed reverted to actual values when less than 85% or greater than 95%. Oxygen saturation targeting with the altered pulse oximetry was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximetry. Adjustments in supplemental oxygen to target oxygen saturations were performed by the clinicians, not by the research staff.

Assessments

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Mortality at any time during hospitalization occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed in both gestational age groups used for stratification. Mortality in the first and second weeks after birth was comparable in the

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DISCUSSION

The recommended ranges of oxygen saturation targeting for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Despite now being based on randomized controlled trials and limited evidence of safety, lower oxygen saturation targeting has become the recommended. In the current trial, lower oxygen saturation targeting (85-89%) resulted in an increased risk of mortality.

This trial was not prospectively powered for a difference in mortality only between the two oxygen saturation groups and, thus, the results should be viewed with caution. However, this is the largest randomized trial to test the effect of lower versus higher oxygen saturation targeting and the results add to previous data raising the concern that oxygen restriction may increase mortality in very preterm

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infants. The infants in this trial were more immature than those of any previous trails of oxygen restriction and, thus, may have had a higher susceptibility to the effects of lower oxygen saturation targeting. In addition, aside from the decreased use of oxygen supplementation at 36 weeks, there were no other benefits from oxygen restriction. The previous data on the increased mortality from oxygen restriction were from studies with lower level of evidence rather than randomized controlled trials, except for the trends in the 1950s which had a combined risk difference of 4.9% increase in mortality in the oxygen restricted group (Ref 1).

Restriction of oxygenation in the randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 94% and 89 to 94% in the lower oxygen saturation group. Mortality in the current trial did not differ by 7 or 14 days. Therefore, the lower target of oxygen saturations rather than the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials that address the same intervention tested in the current trial as well as a planned prospective meta-analysis.[1] At the present time, it is important that these trials continue. It is also important that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. Further information from the ongoing randomized controlled trials that evaluate lower versus higher oxygen saturation targeting will become available in the next years but at the present time, caution should be exercised regarding oxygen targeting in the low range tested in the current trial.

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
Black	258/655 (39)	231/661 (35)
Hispanic	132/655 (20)	127/661 (19)
Other	23/655 (4)	24/661 (4)
Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
5-min Apgar score < 3 – no. (%)	34/655 (5)	24/661 (4)
Surfactant – no.(%)	532/654 (81)	557/659 (85)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Relative Risk (95% CI)
Death before discharge	130/655 (20)	106/661 (16)	
Death by 7 days	41/655 (6)	38/661 (6)	
Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	
Pneumothorax – no. (%)	48/655 (7)	43/661 (7)	
Any air leaks – no. (%)	50/655 (8)	43/661 (7)	

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Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

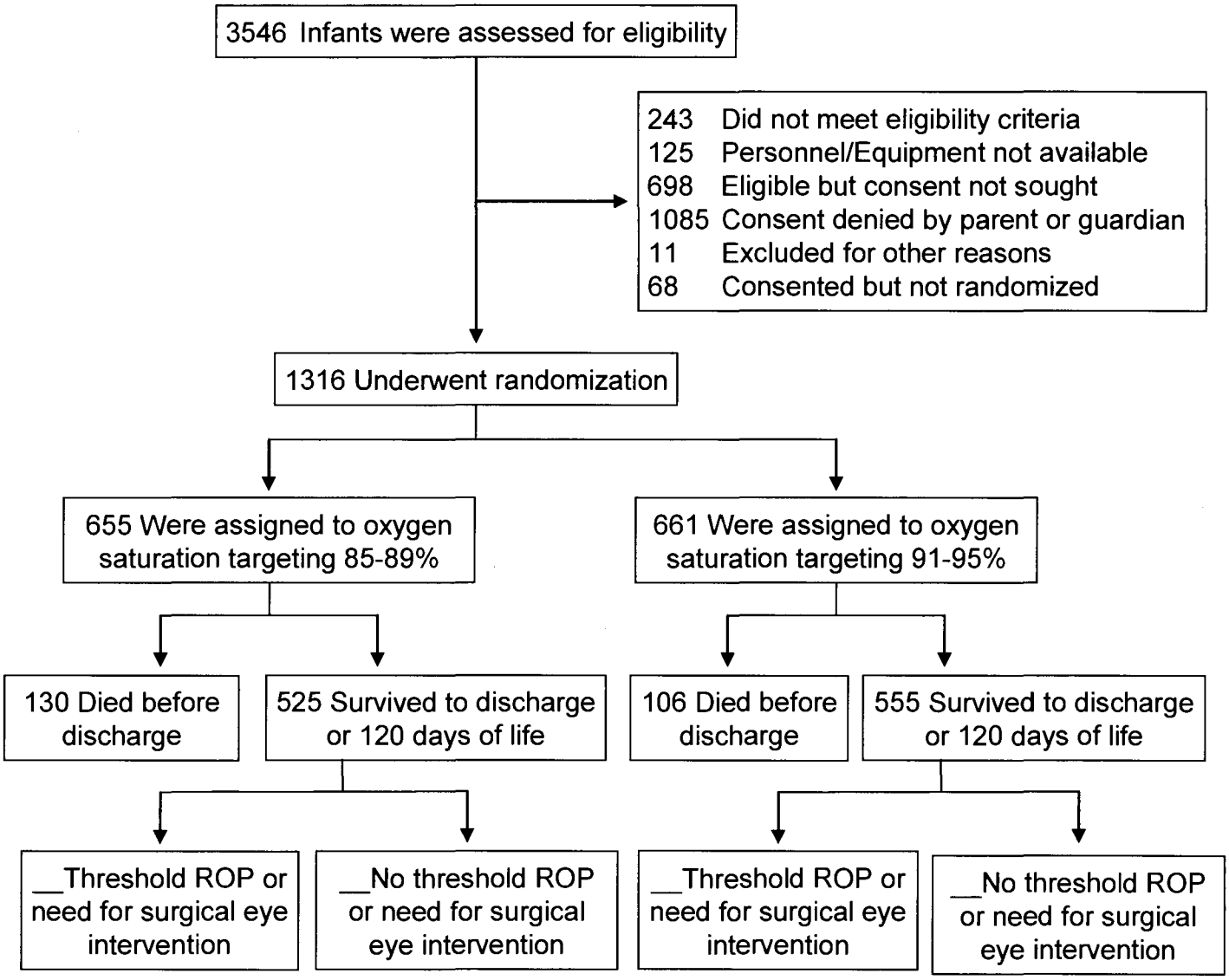

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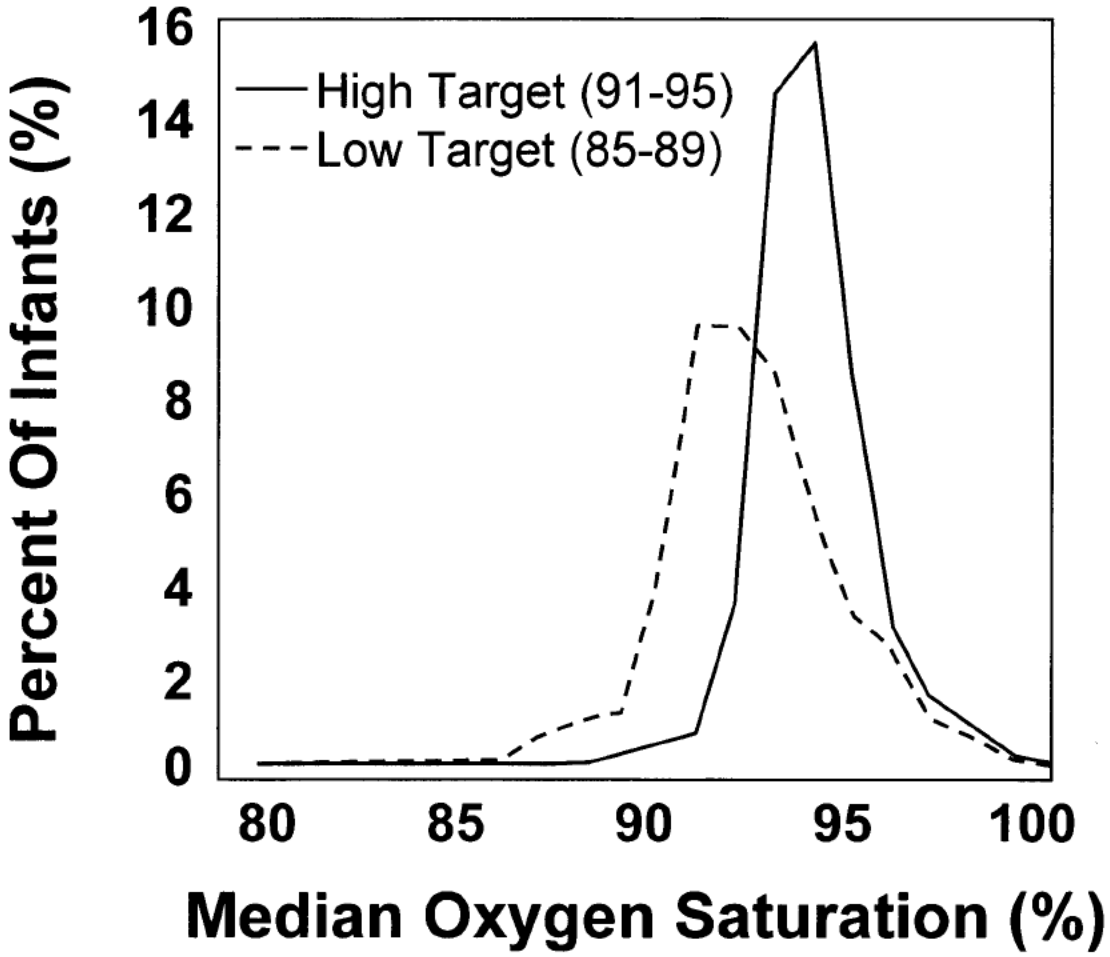
Figure 2



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From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Thursday, September 17, 2009 11:48:44 AM

Yes,
Richard

Higgins, Rosemary (NIH/NICHD) [E] wrote:
>
> As you may recall, Ed Bell had requested to share the SUPPORT protocol
> and forms with Ophthalmology colleagues to develop a secondary
> analysis of the SUPPORT trial data to look at growth and development
> of ROP. I have discussed with Drs. Finer and Duara who are ok with
> this provided the primary analyses and the secondary growth analyses
> are first done. *Send me a yes/no vote to share the forms with Ed's
> colleagues by September 15.*
>
> * *
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal Medicine
>
> Eunice Kennedy Shriver National Institute of Child Health and Human
> Development
>
> National Institutesof Health
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>
> MSC 7510
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>
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>
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> 301-496-3790 (FAX)
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Richard A. Ehrenkranz, MD
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; Das, Abhik
Cc: Wally Carlo, M.D.
Subject: O2 Saturation Paper
Date: Tuesday, September 15, 2009 4:50:09 PM
Attachments: Oxygen Saturation Targeting.9.15.09.doc

Dear Rose, Neil, Marie, and Abhik:

Enclosed is draft 3 of the saturation paper. I have written as agreed (without the ROP data). The Results and Discussion are completely new. The Discussion is still in its first draft. I have completed Figure 1 (pending decision to drop completely the ROP data) and have modified Figure 2 from one of the figures Marie sent. I have used the median figure as it gives one value per baby so there is less bias due to babies on O2 for a prolonged period. Should we consider a survival plot as mortality did not differ on day 7 and may be a late occurrence? The references need formatting.

I think you may want to wait until we are closer to data lock.

Marie: I still need IVH/death and other outcomes (see Tables) as well as RR and CI.

Thanks for your help.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Word count:

Abstract: 93

Manuscript: 1779

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure oxygenation levels lower than previously maintained. However, the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1316 infants of 24 to 27 weeks gestation born at 20 centers of the Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities among prematurely born infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in premature infants in randomized controlled trials performed in the 1950s.[1] However, the practice of restricting oxygen supplementation in subsequent years was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] However, more recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal appear to increase the risk of retinopathy of prematurity.[3-5] Oxygen toxicity may also increase the risk of mortality[6, 7], bronchopulmonary dysplasia[8-10], periventricular leukomalacia[11], cerebral palsy[12], and other morbidities. Even though a multicenter study [13] could not determine an association between oxygen levels and retinopathy, a single center cohort study using transcutaneous oxygen monitoring supported the association retinopathy with exposure to oxygen levels $\geq$ 80mmHg.[14]

With the introduction of pulse oximeters, more recent data are based on oxygen saturations. A survey study of 144 neonatal intensive care units conducted in 2001, revealed that average target oxygen saturations had a low limit of 90% and an upper limit of 96%.[5] Use of high saturation targets may result in increased risk for retinopathy. The rate of retinal ablation surgery was higher at neonatal intensive care units with maximal target oxygen saturation $\geq$ 98% (5.6 $\pm$ 1.1 versus 3.1 $\pm$ 0.3%) or higher than 92% (3.3 $\pm$ 0.3 versus 1.4 $\pm$ 0.2%).[5] Recent studies suggest that oxygen saturation targeting from the first day after birth at levels lower than previously used may reduce the incidence of retinopathy. In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of retinopathy requiring ablation therapy was 27% in units where target saturations were 88 to 98% and 6%

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in units where the target was 70 to 90%.[3] Rates of mortality and cerebral palsy did not differ in these units. In three other studies, a policy of oxygen saturation targeting of approximately 83 to 95% resulted in a substantial reduction in retinopathy.[4, 15, 16] However, actual oxygen saturations achieved were not reported. Pulse oximetry has become the standard technique for continuous monitoring of oxygenation. While data from recent prospective observational and retrospective studies[3, 4, 15-19] suggest that maintenance of oxygenation at ranges lower than previously used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence that these oxygenation levels can reduce retinopathy of prematurity without an increase in serious adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting, testing the effect of a lower oxygen saturation range (85-89%) as compared to a higher oxygen saturation range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. The factorial design allowed comparison of prophylactic/early surfactant versus continuous positive airway pressure; thus, controlling for the approach to ventilatory support.

METHODS

The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

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Infants of $24^{0/7}$ to $27^{6/7}$ weeks without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiples were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks) and by center. Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% with masking using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[20] They were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy. The oxygen saturation values displayed reverted to actual values when less than 85% or greater than 95%. Saturation targeting was initiated within the first two hours after birth. Oxygen saturation targeting with the altered pulse oximetry was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen supplementation before 36 weeks post-menstrual age were placed back on the assigned study pulse oximetry. Adjustments in supplemental oxygen to target oxygen saturations were performed by the clinicians, not by the research staff.

Assessments

Research nurses recorded all data using standardized definitions. Data were collected until discharge or 120 days postnatal age whichever occurred last. Threshold retinopathy of prematurity (New Type 1

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threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[21]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1: Stage 3 retinopathy of prematurity, even without plus disease

Plus disease with any stage retinopathy of prematurity

If in zone II: Plus disease with stage 2 retinopathy of prematurity

Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Outcomes included predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of this factorial trial was a logistic regression analysis of the percentages of infants in each group (lower versus higher oxygen saturations) who developed the primary outcome. An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1312 infants for 80% power and a baseline estimated rate of 45% of death/threshold retinopathy/surgery, and based on an increase by a factor of 1.12 to account for randomizing multiples to the same treatment group and an increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. The trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted by the staff at the data center. A two-sided P value of less than 0.05 was considered to statistically significant. Analyses did not include adjustment for multiple comparisons. An independent data safety and monitoring committee reviewed the primary outcomes,

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adverse events, and other interim results at ~25%, 50%, and 75% of planned enrollment. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

RESULTS

1316 infants were enrolled between January 2004 and March 2009 (Figure 1). Enrollment was temporarily stopped by the Data Safety and Monitoring Committee because of concerns regarding compliance with oxygen saturation targets. Separate of analysis of the oximetry data while on room air versus while on oxygen supplementation resolved the concerns. The baseline characteristics of the lower saturation group and the higher saturation group were similar (Table 1).

Major outcomes

The Data Safety and Monitoring Committee masked interim analyses were made available to the investigators after enrollment was completed. There had been a trend for increased mortality in one of the treatment groups that had not reached the stopping boundary. The principal investigator and data center staff undertook a safety analysis to evaluate potential adverse outcomes without unblinding the retinopathy outcome data. This manuscript reports the hospital outcomes. Retinopathy and 18-22 month follow up outcomes will be reported later.

Mortality at any time while hospitalized occurred in 130 of the 655 (20%) of the infants in the lower oxygen saturation group versus in 106 of the 661 (16%) of the infants in the higher oxygen saturation group (RR 0.78, CI 0.62, 0.99, P=0.04). Comparable results were observed in both gestational age groups used for stratification. Mortality in the first and second weeks after birth was comparable in the

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two groups (Table 2). Other prespecified major outcomes were comparable between the two treatment groups (Table 2).

The median oxygen saturation of both groups differed substantially but, as expected, there was some overlap (Figure 2). These data indicate that actual oxygen saturation levels are slightly higher than targets in both treatment groups. The duration of oxygen supplementation was shorter in the lower oxygen saturation group but the duration of mechanical ventilation, continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation did not differ (Table 3). Other measures of resource utilization did not differ.

DISCUSSION

The ranges of oxygen saturation targeting recommended for very preterm infants have been determined from nonrandomized studies and restriction of oxygen supplementation is becoming the standard practice.[3, 22] However, there was an increase in mortality when a restrictive oxygen supplementation was practiced in the 1950s and 1960s. Lower oxygen saturation targeting has become the recommended even though this practice is not based on randomized controlled trials and there has been limited evidence of safety. In the current trial, lower oxygen saturation targeting (85-89%) resulted in an increased risk of mortality.

This trial was not powered for mortality only and thus caution should be exercised regarding the mortality data. However, this is a large multicenter trial and the results extend previous data raising the

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concern that oxygen restriction may increase mortality in very preterm infants. The previous data were from studies with lower level of evidence rather than randomized controlled trials.

Restriction of oxygenation in the randomized controlled trials in preterm infants beyond the first weeks of life did not show trends for increased mortality in the lower saturation target groups.[17, 18] However, these trials aimed for saturations of 91 to 95% and 89 to 94% in the lower oxygen saturation group. Mortality in the current trial did not differ by 7 or 14 days so the lower target of oxygen saturations used rather than the postnatal age of the intervention may be related to the adverse outcome.

There are several ongoing trials that address the same intervention tested in the current trial as well as a planned prospective meta-analysis (ref). At the present time, it is important that these trials continue. It is also important that the investigators and the data safety and monitoring committees of these trials are aware of the results of the current trial so appropriate decisions can be made regarding their interim analyses, completion of the trials, and dissemination of the data. The current trial raises the concern of adverse hospital outcomes due to oxygen saturation targeting in the 85 to 89% range. While further data from the ongoing randomized controlled trials are available, caution should be exercised regarding oxygen targeting in this range.

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Table 1. Baseline Characteristics of the Patients

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Birthweight – g (m±SD)	835±193	825±193
Gestational age – wk (m±SD)	26±1	26±1
Male sex – no. (%)	342/655 (52)	370/661 (56)
Race or ethnic group – no. (%)		
White	242/655 (37)	279/661 (42)
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Antenatal corticosteriods (any) – no. (%)	634/655 (97)	631/660 (96)
Antenatal corticosteroids (full course) – no. (%)	478/652 (73)	460/657 (70)
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Death by 14 days	64/655 (10)	56/661 (8)	
Bronchopulmonary dysplasia by O_2 use at 36 weeks*	203/541 (38)	262/567 (46)	
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*	317/655 (48)	356/661 (54)	
Bronchopulmonary dysplasia (physiologic) at 36 weeks*	209/542 (39)	239/567 (42)	
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*	322/655 (49)	333/661 (50)	
Intraventricular hemorrhage, grade 3 or 4	95/632 (15)	87/639 (14)	
Intraventricular hemorrhage, grade 3 or 4 or death	188/655 (29)	161/660 (24)	
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/661 (20)	
Necrotizing enterocolitis, stage ≥ 2	76/642 (12)	70/648 (11)	
Necrotizing enterocolitis, stage ≥ 2 or death	176/655 (27)	155/661 (23)	
Late onset sepsis	228/625 (36)	227/633 (36)	
Late onset sepsis or death	301/655 (46)	291/661 (44)	
Patent ductus arteriosus	308/642 (48)	323/647 (50)	
Medical treatment for patent ductus arteriosus	220/635 (35)	232/644 (36)	
Surgical treatment for patent ductus arteriosus	73/642 (11)	68/647 (11)	
Pneumothorax – no. (%)	48/655 (7)	43/661 (7)	
Any air leaks – no. (%)	50/655 (8)	43/661 (7)	

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Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/643 (11)

* In babies alive at 36 weeks post-menstrual age.

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Table 3. Other Outcomes

Characteristic	Lower Saturation Group	Higher Saturation Group	P value
Length of stay any hospital, (days) m+SD	99±39	102±43	0.17
Length of stay NRN hospital, (days) m+SD	95±41	99±44	0.0808
Duration of mechanical ventilation, (days) m+SD	21±25	23±25	0.2095
Duration of oxygen supplementation, (days) m+SD	52±38	61±37	0.0002
Continuous positive airway pressure, (days) m+SD	16±14	16±14	0.9483
Nasal synchronized intermittent mandatory ventilation, (days) m+SD	3±7	4±7	0.0615
Alive off mechanical ventilation by day 14, (days) m+SD	331/643 (51)	322/649 (50)	0.5031
Alive off mechanical ventilation by day 7, (days) m+SD			

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Figure 1

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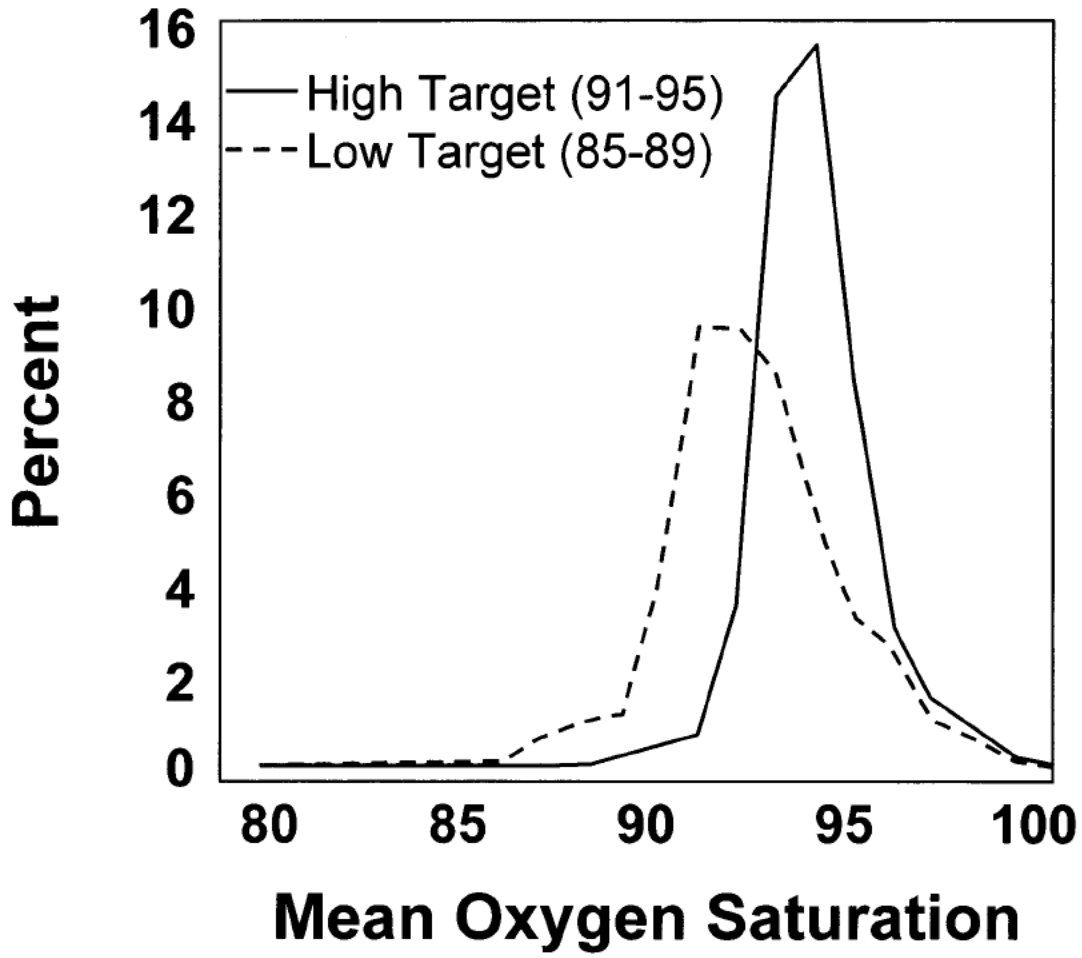
Figure 2



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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Huitema, Carolyn Petrie
Subject: Duke Site Visit (Monitoring) Report
Date: Tuesday, September 15, 2009 4:26:16 PM
Attachments: Support Monitor Report Duke 20090915.doc

Hi Rose,

Please find attached our final draft of the Duke Monitoring trip report. I focused solely on the data monitoring and regulatory rather than any of the communications or lack of processes in place to bring things up to speed because I believe that will be covered in the trip on the 29th .

Thanks and please let me know if you have any questions or require any edits.
Kris

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SITE MONITORING TRIP REPORT

Trial Name:	The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants The SUPPORT Trial
Site Number:	19
Site Name:	Duke University
Investigator Name:	Ronald Goldberg MD
Prior Monitoring Visits:	December 3, 2002; March 19, 2008
Date(s) of This Visit:	September 2 & 3, 2009

Monitor Name: Kristin Zaterka-Baxter, RN
Other Non-Site Personnel in Attendance: Jeanette Auman, B.S Amanda Irene, B.S Jamie Newman, PhD Carolyn Huitema, M.S.
Site Personnel in Attendance: Ronald Goldberg, MD Michael Cotton, MD Kimberly Fischer, PhD Stephanie Crosby, LPN Charles Vajdl

Monitoring Summary:

Monitoring of primary study outcomes (ROP, BPD, 18-22M Follow Up) was incomplete due to lack of source documentation and was overall unsuccessful due to more than three of the 15 cases determined to have one or more data inconsistencies.

- ROP source documents were missing or incomplete for 11 of the 15 cases reviewed. There were at least 2 inconsistencies reported for final ROP status based on source document review.
- BPD data was available though found to be inconsistent with source documents in several cases. In at least 4 cases BPD queries were generated for incomplete data on the Supp11 because these infants were transferred to Durham Regional Hospital (DRH) prior to 36 weeks and no further data was collected. However, final status per the GDB was documented as discharged to home after 36 weeks; it is unclear whether DRH is a participating site and whether Duke can obtain data from DRH.
- There are no outstanding issues with Follow-Up for the cases reviewed. The follow up rate for both Support and GDB averages 93%.

Data edits were reviewed by the RTI Data Manager with the Duke staff. Most of the outstanding data edits for Support were resolved within this 2 hour window of review. Edits are repeatedly reported from month to month because they are not being resolved expeditiously; noted that there are a minimal number of Support edits.

The Regulatory process at Duke is quite involved with numerous (5) levels of review prior to approval. Average time from submission to approval is 2 months. All recent studies have been submitted or approved. There is a detailed audit trail from submission to approval available for each study. There were a few informed consents for the Breathing Outcomes secondary study that were not readily available for review and 2 incomplete Support consent forms specifically for the embedded opt-in/opt-out Neuroimaging and Neurodevelopmental secondary study option.

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A. Regulatory Oversight

1. Local regulatory oversight adherence ☑ Yes ☐ No
- IRB Submission and approval adequately documented

- Detailed outline and discussion regarding regulatory processes for NIH approved studies recommended to enhance timely protocol approvals.

In brief; five levels of review are required before a study can start at Duke.
-Department Administrator
-Department Chair review
-Departmental IRB review
-Pediatric Risk Assessment review
-Full IRB review

Protocol	Study Approved for IRB Submission	Date of Submission to Local IRB	IRB Final Approval	Expires
GDB		3/23/2009	5/5/2009	5/19/2010
GDB Follow Up		2/26/2009	3/31/2009	4/21/2010
SUPPORT		2/10/2009	3/11/2009	4/7/2010
Term Hypotension		4/20/2009	5/28/2009	5/28/2010
Preemie aEEG	5/21/2009	6/4/2009	8/7/2009	8/7/2010
Early BP	5/21/2009	6/11/2009	Pending	
Late Hypothermia		4/2/2009	5/14/2009	5/29/2010
Extended Hypo FU		10/21/2008	11/18/2008	12/14/2009

All studies approved have current IRB approval. The regulatory binder presented did not have the following current documents:

Protocol	Items Missing
GDB	consent form in English technical memos (18, 29, 20, 23)
GDB Follow Up	consent form in English, Manual of operations technical memos (21, 33, 34)
SUPPORT	consent form
Growth:	protocol
Breathing Outcomes:	consent eventually rolled into primary
Neuroimaging:	Manual of operations consent eventually rolled into primary
Term Hypotension	Manual of operations
Preemie aEEG	Technical memo (1)
Early BP	*pending IRB approval*
Late Hypothermia	Manual of operations IRB approval Consent form technical memo (2)
Extended Hypo FU	consent form

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B. Cases Reviewed:

CENTER	NETWORK	DOB
19	69841	09/07/2005
19	69871	09/16/2005
19	69971	09/30/2005
19	71681	11/28/2006
19	72361	06/06/2007
19	72362	06/06/2007
19	72541	05/21/2007
19	72892	09/26/2007
19	72911	10/01/2007
19	72981	10/27/2007
19	72982	10/27/2007
19	73981	11/29/2008
19	74031	12/22/2008
19	74032	12/22/2008
19	74131	01/18/2009

C. General Study Conduct

1. The Investigator is adhering to the protocol and amendments ☑ Yes ☐ No
- All subjects reviewed were randomized and delivered the assigned intervention however based on randomization number however, 2 cases reviewed were missing the actual randomization cards to verify the site used the correct randomization number.
- All subjects reviewed followed intervention guidelines per treatment arm and protocol.

2. Subject eligibility ☑ Yes ☐ No
- All subject that were reviewed appeared to be eligible for study however, of the 15 cases, 4 medical record charts were incomplete or unavailable for source documentation (69971, 74031, 74032, 73981)

D. Data Management

Support Study Data Collection

1. Case Report Forms (CRFs) reviewed against source documentation ☑ Yes ☐No
CRFs were reviewed where source documentation was provided

2. Source documentation adequate to support entries on CRFs ☐ Yes ☑No
Many source documents were not available at the time of review. There was an adoption of electronic medical records in 2008 though neither the electronic records nor paper medical records contained complete source documentation.

Several data inconsistencies noted when reviewed against available source documents (as outlined below).

3. Timely data entry ☐ Yes ☑ No
Upon random review of the Support data entry one infant was identified as being enrolled to study on 03/26/07; no data was entered until 09/02/09 (ID 74261) post completion of recruitment.

4. Timely resolution of edits ☐ Yes ☑No
- As of the most recent SUMMARY OF MISSING SUPPORT FORMS report posted to the NRN website (09/05/09), 30 out of a total of 64 missing forms cross centers belonged to Duke, the Supp05 forms had the

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highest number missing (N17). The average of missing Support forms cross centers is 3 (range 0-8).

- Within the batch edits posted to the NRN website there are a minimal number of edited reported however, over the past 3 months, an average of 80% of these edits have been unresolved and repeated from month to month.

5. Deviations Noted ☑ Yes ☐ No

- Infant (74131) withdrawn from study per physician decision due to unblinding of the oximetery arm on DOL 51. Protocol Deviation form SUPP09 completed 03/26/09 however there is no documentation of informing NICHD or RTI of withdrawal and no source documentation of withdrawal or parental notification of withdrawal in medical or research records. Discussion of this case and whether the data can be used is pending.

E. Secondary Studies Data Collection

1. Object Permanence Ancillary (MRI09A form completed appropriately for eligible subject) ☐ Yes ☑ No
Jamie Newman, RTI Follow-up Coordinator, reviewed the Monthly Report table and accompanying list of eligible patients posted to the site specific portion of the NRN website with Dr. Kim Fisher. Out of 18 patients enrolled in the Neurodevelopmental Outcomes Secondary to SUPPORT, 5 patients are currently expected for the Object Permanence Ancillary (pts that have already been seen for 18 month Follow-up and have a Bayley III exam). No MRI09A forms have been keyed to date. Jamie will also address this with the Bayley examiner, Dr. Katie Gustafson. Duke is well positioned for moving forward with this study since the windows are just starting to open. They should be able to collect these additional Bayely III items (items 40, 45, 50) prospectively for the remainder of their patients. Whether the additional Bayley III items can be collected from the original Bayley III score form for the 5 patients that have already been seen for follow-up will be discussed with the Bayley examiner.

2. Tracking for SUPPORT School Age (SEF01 form completed appropriately for eligible subjects) ☐ Yes ☑ No

Out of 12 patients with a successful MRI for the Neurodevelopmental Outcomes Secondary to SUPPORT, only 1 patient is currently expected to have an SEF01 form keyed, which is the 3-4 year tracking form. However, Duke is well positioned for moving forward with tracking for this study since the 3-4 year tracking windows are just starting to open. Tracking tools and open window reports can be printed from the Network computer.

3. Breathing Outcomes questionnaires completed appropriately for eligible subject) ☐ Yes ☑ No
Duke does the discharge interviews face-to-face and Rochester conducts the 6, 12, and 18 month interviews. All SUPPORT/Breathing Outcomes patients have been discharged. During staff turnover (coordinators) at Duke there may have been delays in getting contact information to Rochester for conducting the interviews which may have contributed to the missing 6 months interviews (all 6 month interviews). Because Breathing Outcomes interviews can not be done out of window, making sure Rochester has contact information for remaining interviews will need to be done.

Breathing Outcomes eligible patients that are missing Breathing Outcomes consent forms needs to be further investigated (perhaps not all of the patient's file was given to us?). One possibility is that the family refused and the enrollment log (SUPF00) has not been keyed to indicate this. This is where the coordinator/keyer indicates that patient refused consent. (consent granted = 2 NO or 3 refused).

The enrollment log is located on the NRN website:
Protocols – SUPPORT – Secondary Studies – Breathing Outcomes – Forms – SUPF00 (Enrollment Log)
This will be the first page that appears when the keyer begins to key Breathing Outcomes data. Once patients that refuse have been keyed on the enrollment log, they will no longer appear on the Breathing Outcomes Interview Schedule Report.

4. Neuroimaging and Neurodevelopmental Outcomes form MRI01 completed appropriately for eligible subject and required images sent to RTI. ☐ Yes ☑ No
Several MRI01 forms are outstanding; this form is to be completed regardless of whether this infant in enrolled to

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the secondary. For the MRI01 forms completed, the majority of the previous data inconsistencies have been resolved prior to the monitoring visit. There remain 2 outstanding MRI images that should be sent to RTI as soon as possible (ID 72101, 72051)

5. SUPPORT Follow-up ☑ Yes ☐ No
Duke has a high SUPPORT Follow-up rate of 92.59% (based on form completion as well as official follow-up rate). Out of 27 SUPPORT patients currently expected for follow-up, 25 patients have completed follow-up, 2 patients have died after discharge and 2 patients are lost-to-follow-up. No inappropriate form completion was noted.

6. GDB Follow-up ☑ Yes ☐ No
Duke has a high GDB Follow-up rate of 93.33% (based on form completion as well as official follow-up rate). Out of 30 patients currently expected for follow-up, 28 patients have completed follow-up, 1 patient is lost-to-follow-up, and 1 patient is pending. No inappropriate form completion was noted.

7. Antenatal Secondary study ☐ Yes ☐ No ☑ NA
Data on this study was not reviewed

8. Growth Outcomes Secondary study ☐ Yes ☐ No ☑ NA
Data on this study was not reviewed

F. List issues that require follow-up

1. Verification of all Support Trial primary outcome data (64 cases) is requested.
2. Resolution of all Support Trial data edits and inconsistencies is requested: all edits/inconsistencies reported below, all edits posted to the NRN site specific website; all recent BPD queries; all recent Cross-Forms queries.
3. Confirmation of ancillary site participation for the following sites is requested: Durham Regional Hospital (DRH); Raleigh Duke Health; Alamance Regional Medical Center
4. Regulatory follow-up; Duke should track and maintain all study approvals and approved consent forms where applicable and submit these to RTI/NICHD as soon as approval is granted (including all satellite site approvals and approved consents were applicable).
    a. Follow up regarding unavailable or inappropriate MRI and Breathing outcomes consent is requested.
5. Standard Operating Procedures should be developed and adhered to for; data QA/QC; edit resolution; ancillary site communication, regulatory affairs process and procedures; protocol and data management training.
6. Follow-up with Rochester regarding the Support Secondary Breathing Outcomes eligible study subjects is recommended.

G. Case Audit

1. Patient NRN ID 6984-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	☐ Yes ✓ No
3a. SUPPORT Growth consent signed	☐ Yes ☐ No ✓ NA

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4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ✓ Yes ☐ No ☐ NA

5. SUPPORT Neuroimaging enrolled? ☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ☐ No ✓ NA

6. Follow Up window open? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓ No
2. Were there any problems with the eye exams? ✓ Yes ☐ No
   a. If yes, explain

issues with ROP exam dates not matching dates on Supp10 form

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ☐ Yes ✓ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

d/c to DRH 11/15/05- status d/c to home 12/12 – cannot verify BPD outcome

d. Other

- checked for eligibility and protocol procedure; no issues
-Need copy of dc summary

2. Patient NRN ID 6987-1

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No
(witness unrelated to study section not signed)
2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ☐ Yes ✓ No
3a. SUPPORT Growth consent signed ☐ Yes ☐ No ✓ NA

4. SUPPORT Breathing Outcomes enrolled? ☐ Yes ✓No
4a. SUPPORT Breathing Outcomes consent signed ☐ Yes ☐ No ✓ NA

5. SUPPORT Neuroimaging enrolled? ☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ☐ No ✓ NA

6. Follow Up window open/closed? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA

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b. ROP Outcome

1. Were all eye exams available for review? ✓ Yes ☐ No
2. Were there any problems with the eye exams? ☐ Yes ✓ No
   a. If yes, explain

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ☐ Yes ✓ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

d/c to DRH 11/07/05- status d/c to home 12/02 – cannot verify BPD outcome

d. Other

- Checked for eligibility and protocol procedure; no issues
-Need copy of dc summary
-No note in comp with 11/7/05-dc from Duke to DRH on 11/7/05 but per NG03, status=DC to home 12/2/05. Do have SUPP11 data from DRH

3. Patient NRN ID 6997-1

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No
did not check section with question pertaining to being contacted @18 months, baby died
2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ☐ Yes ✓ No
3a. SUPPORT Growth consent signed ☐ Yes ☐ No ✓ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00
5. SUPPORT Neuroimaging enrolled? ☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ☐ No ✓ NA

6. Follow Up window open/closed? ✓ Yes ☐ No
6a. Follow Up consent signed ☐ Yes ☐ No ✓ NA
baby died

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓No
2. Were there any problems with the eye exams? ✓ Yes ☐ No
   a. If yes, explain

Missing 6 ROP exam reports

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Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ☐ Yes ✓ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

- has NICU discharge summary but not detailed enough
- BPD 36wk support verified, no BPD

d. Other

No SUPP02 entered
This infant died 2/21/2006, after discharge

4. Patient NRN ID 7168-1

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No

2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ✓ Yes ☐ No
3a. SUPPORT Growth consent signed ✓ Yes ☐ No ☐ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00
5. SUPPORT Neuroimaging enrolled? ☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ☐ No ✓ NA

6. Follow Up window open/closed? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓ No
2. Were there any problems with the eye exams? ✓ Yes ☐ No
   a. If yes, explain

Missing 2 ROP exam reports (has 2 out of 4)

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ☐ Yes ✓ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

d/c to DRH 1/23/07, status dc to home 3/12/07 – cannot verify BPD outcome

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d. Other

SUPP11 only to 1/23/07 with NC support

5. Patient NRN ID 7236-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed	☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00	
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed	☐ Yes ☐ No ✓ NA
6. Follow Up window open/closed?	✓ Yes ☐ No
6a. Follow Up consent signed	✓ Yes ☐ No ☐ NA

b. ROP Outcome

1. Were all eye exams available for review?	☐ Yes ✓ No
2. Were there any problems with the eye exams?	✓ Yes ☐ No
a. If yes, explain	

Missing all ROP exam reports

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	☐ Yes ✓ No
2. Were there any problems with the data?	✓ Yes ☐ No
a. If yes, explain	

transferred prior to 36 wk date

d. Other

- checked for eligibility and protocol procedure; no issues

6. Patient NRN ID 7236-2

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No

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2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed	☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00	
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed	☐ Yes ☐ No ✓ NA
6. Follow Up window open/closed?	✓ Yes ☐ No
6a. Follow Up consent signed	✓ Yes ☐ No ☐ NA

b. ROP Outcome

1. Were all eye exams available for review?	☐ Yes ✓ No
2. Were there any problems with the eye exams?	✓ Yes ☐ No
a. If yes, explain	

Missing all ROP exam reports

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	☐ Yes ✓ No
2. Were there any problems with the data?	✓ Yes ☐ No
a. If yes, explain	

transferred prior to 36 wk date

d. Other

- checked for eligibility and protocol procedure; no issues

7. Patient NRN ID 7254-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	☐ Yes ✓ No
4a. SUPPORT Breathing Outcomes consent signed	☐ Yes ☐ No ✓ NA
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed	☐ Yes ☐ No ✓ NA

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6. Follow Up window open? ✓ Yes ☐ No
6a. Follow Up consent signed ☐ Yes ☐ No ✓ NA
per NF10 Lost to FU, non-compliant, no NF12 entered for pt

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓ No
2. Were there any problems with the available eye exams? ✓ Yes ☐ No
   a. If yes, explain

-values from exam do not match Supp10 from exam dated 7/17
-additional ROP exam report dates 8/29 that is not noted on Supp10 but is located within chart

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ✓ Yes ☐ No
2. Were there any problems with the data? ☐ Yes ✓ No
   a. If yes, explain

- BPD verified 36 wk data, no BPD, did not need to be challenged

d. Other

- checked for eligibility and protocol procedure; no issues

8. Patient NRN ID 7289-2

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No
witness unrelated to study section not signed
2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ✓ Yes ☐ No
3a. SUPPORT Growth consent signed ✓ Yes ☐ No ☐ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00
5. SUPPORT Neuroimaging enrolled? ✓ Yes ☐ No
5a. SUPPORT Neuroimaging consent signed ✓ Yes ☐ No ☐ NA
Signed consent in MR; separate form enrolled per MRI01
6. Follow Up window open? ✓ Yes ☐ No
6a. Follow Up consent signed ☐ Yes ✓ No ☐ NA
No F/U folder-at the time of audit, FU window open 6/23/2009 – 11/7/2009

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b. ROP Outcome

1. Were all eye exams available for review? ✓ Yes ☐ No
2. Were there any problems with the available eye exams? ✓ Yes ☐ No
   a. If yes, explain

- issue with date not matching Supp10 date for first exam report (in DMS as 10/30/2007)

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ✓ Yes ☐ No
2. Were there any problems with the data? ☐ Yes ✓ No
   a. If yes, explain

- BPD verified 36 wk data, on room air, did not need to be challenged

d. Other

9. Patient NRN ID 7291-1

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No
witness unrelated to study section not signed
2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ✓ Yes ☐ No
3a. SUPPORT Growth consent signed ✓ Yes ☐ No ☐ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ☐ Yes ✓ No ☐ NA
Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00
5. SUPPORT Neuroimaging enrolled? ✓ Yes ☐ No
5a. SUPPORT Neuroimaging consent signed ✓ Yes ☐ No ☐ NA
Signed Consent in MR; separate form, enrolled per MRI01
6. Follow Up window open/closed? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓ No
2. Were there any problems with the available eye exams? ✓ Yes ☐ No
   a. If yes, explain

- missing 2 ROP exam reports (11/30 and 12/14, note waiting for final opth. Result)
- date mismatch on ROP exam from 10/13 (recorded as 11/13 on ROP exam report)
- Zone/Stage data does not match on Supp10 forms and ROP exam report from

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exam dated 10/30

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ☐ Yes ✓ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

-transferred to DRH 11/25/07, dc to home as status 12/07 – cannot verify BPD outcome
-Supp11 data ends 11/25/07, readmitted

d. Other

- checked for eligibility and protocol procedure; no issues
-Need NICU dc summary

10. Patient NRN ID 7298-1

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No

2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ✓ Yes ☐ No
3a. SUPPORT Growth consent signed ✓ Yes ☐ No ☐ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ✓ Yes ☐ No ☐ NA
checked ok to be contacted
5. SUPPORT Neuroimaging enrolled? ✓Yes ☐ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ✓ No ☐ NA
Signed Consent form (embedded) in MR; did NOT agree. Listed as Enrolled per MRI01, site should fill out MRI01 Q.A.1 as "No"
6. Follow Up window open? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA
FU window currently open 8/13/2009 – 12/28/2009

b. ROP Outcome

1. Were all eye exams available for review? ☐ Yes ✓ No
2. Were there any problems with the available eye exams? ✓ Yes ☐ No
   a. If yes, explain

- Missing 1 ROP exam report (has 15 of 16)

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

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c. BPD Outcome

1. Were all pertinent data available for review? ✓ Yes ☐ No
2. Were there any problems with the data? ☐ Yes ✓ No
   a. If yes, explain

- BPD verified 36 wk data, on room air, did not need to be challenged

d. Other

- checked for eligibility and protocol procedure; no issues

11. Patient NRN ID 7298-2

a. Consent

1. GDB enrolled? ✓ Yes ☐ No
1a. GDB consent signed ✓ Yes ☐ No
In MR
2. SUPPORT primary enrolled? ✓ Yes ☐ No
2a. SUPPORT primary consent signed ✓ Yes ☐ No

3. SUPPORT Growth enrolled? ✓ Yes ☐ No
3a. SUPPORT Growth consent signed ✓ Yes ☐ No ☐ NA

4. SUPPORT Breathing Outcomes enrolled? ✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed ✓ Yes ☐ No ☐ NA
embedded, in MR; checked ok to contact
5. SUPPORT Neuroimaging enrolled? ☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed ☐ Yes ☐ No ✓ NA
No MRI01, embedded; did NOT agree. Site should fill out MRI01 Q.A.1 as "No"
6. Follow Up window open? ✓ Yes ☐ No
6a. Follow Up consent signed ✓ Yes ☐ No ☐ NA
FU window open 8/13/2009 – 12/28/2009

b. ROP Outcome

1. Were all eye exams available for review? ✓ Yes ☐ No
2. Were there any problems with the available eye exams? ☐ Yes ✓ No
   a. If yes, explain

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review? ✓ Yes ☐ No
2. Were there any problems with the data? ✓ Yes ☐ No
   a. If yes, explain

- Incorrect data entered on SUPP05
(11/6/2007 @ 0800 FiO2 entered as 0.21, in MR 0.25 and @ 1000 FiO2 entered as 0.21, in MR 0.22)
(11/7/2007 @ 2400 FiO2 entered as 0.25, in MR 2300 FiO2 was 0.25 and for 2400

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FiO2 was 0.27)
(11/8/2007 @ 2400 FiO2 entered as 0.35, in MR 2300 FiO2 was 0.35 and for 2400 FiO2 was 0.28)

- BPD verified 36 wk data, on room air, did not need to be challenged

d. Other

- checked for eligibility and protocol procedure; issues:
- NO randomization card included in folder

12. Patient NRN ID 7398-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed *embedded with SUPPORT/GROWTH consent form; checked "ok to contact"*	✓ Yes ☐ No ☐ NA
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed *No MRI01; signed consent form, embedded; agree to study*	✓ Yes ☐ No ☐ NA
6. Follow Up window open?	☐ Yes ✓ No
6a. Follow Up consent signed *No F/U consent form- F/U window not open*	☐ Yes ☐ No ✓ NA

b. ROP Outcome

1. Were all eye exams available for review?	✓ Yes ☐ No
2. Were there any problems with the available eye exams?	☐ Yes ✓ No
a. If yes, explain	

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	✓ Yes ☐ No
2. Were there any problems with the data?	☐ Yes ✓ No
a. If yes, explain	

- BPD confirmed on RA at 36wk

d. Other

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- Treatment assignment ok - extubation, OK per ABG on 11/29/2008

13. Patient NRN ID 7403-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed	☐ Yes ✓ No ☐ NA
(embedded in SUPPORT/Growth consent form); Question not answered about being contacted. Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00	
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed	☐ Yes ✓ No ☐ NA
No MRI01; signed consent form; embedded, did not answer question. If infant in not participating, site should fill out MRI01 Q.A.1 as "No"	
6. Follow Up window open?	☐ Yes ✓ No
6a. Follow Up consent signed	☐ Yes ☐ No ✓ NA
No F/U consent form- window not open	

b. ROP Outcome

1. Were all eye exams available for review?	☐ Yes ✓ No
2. Were there any problems with the available eye exams?	✓ Yes ☐ No
a. If yes, explain	

- Inconsistency with ROP outcome per Supp10 data last exam on 03/03/09; per NICU DC summary infant with laser surgery in OS 03/17/09 and stage III Plus Dz 03/28/09
- Missing all ROP exam reports

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	✓ Yes ☐ No
2. Were there any problems with the data?	☐ Yes ✓ No
a. If yes, explain	

- BPD verified 36 wk data, on room air, did not need to be challenged

d. Other

- checked for eligibility and protocol procedure; issues:

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- No Randomization card
- No medical charts
- Randomization to CPAP Intubation in DR with surf d/t poor effort and desats
-Surfactant servanta x2 (within 1hr??) Need MAR for time Surf given

14. Patient NRN ID 7403-2

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed *(embedded in SUPPORT/Growth consent form); question not answered about being contacted. Listed as Enrolled in the DMS but perhaps site failed to enter infant as "Consent Not Granted" on SUPF00*	☐ Yes ✓ No ☐ NA
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed *No MRI01; signed consent form (embedded); did not answer question. If infant in not participating, site should fill out MRI01 Q.A.1 as "No*	☐ Yes ✓ No ☐ NA
6. Follow Up window open?	☐ Yes ✓ No
6a. Follow Up consent signed *No F/U consent form- window not open*	☐ Yes ☐ No ✓ NA

b. ROP Outcome

1. Were all eye exams available for review?	☐ Yes ✓ No
2. Were there any problems with the available eye exams?	✓ Yes ☐ No
a. If yes, explain	

- missing all ROP exam reports

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	✓ Yes ☐ No
2. Were there any problems with the data?	☐ Yes ✓ No
a. If yes, explain	

- BPD verified 36 wk data, on room air, did not need to be challenged

d. Other

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15. Patient NRN ID 7413-1

a. Consent

1. GDB enrolled?	✓ Yes ☐ No
1a. GDB consent signed	✓ Yes ☐ No
2. SUPPORT primary enrolled?	✓ Yes ☐ No
2a. SUPPORT primary consent signed	✓ Yes ☐ No
3. SUPPORT Growth enrolled?	✓ Yes ☐ No
3a. SUPPORT Growth consent signed	✓ Yes ☐ No ☐ NA
4. SUPPORT Breathing Outcomes enrolled?	✓ Yes ☐ No
4a. SUPPORT Breathing Outcomes consent signed	✓ Yes ☐ No ☐ NA
Signed BO consent form (embedded); checked "ok to be contacted	
5. SUPPORT Neuroimaging enrolled?	☐ Yes ✓ No
5a. SUPPORT Neuroimaging consent signed	✓ Yes ☐ No ☐ NA
No MRI01; signed consent form (embedded); agree to study	
6. Follow Up window open?	☐ Yes ✓ No
6a. Follow Up consent signed	☐ Yes ☐ No ✓ NA
No F/U consent form- window not open	

b. ROP Outcome

1. Were all eye exams available for review?	☐ Yes ✓ No
2. Were there any problems with the available eye exams?	✓ Yes ☐ No
a. If yes, explain	

will check ROP in coming days
- No Supp10 form because data recently keyed;

Subsequent medical review of ROP data will be conducted by the NICHD Program officer.

c. BPD Outcome

1. Were all pertinent data available for review?	✓ Yes ☐ No
2. Were there any problems with the data?	✓ Yes ☐ No
a. If yes, explain	

baby was on RA at status but listed FiO2 as 0.33. Incorrect data entered.

d. Other problems

- No SUPP forms entered prior to audit
- Status keyed as in hospital at 120 days 5/17/2009

-Infant keyed as withdrawn from study (SUPP06), neither NICHD nor RTI notified. Protocol Violation was appropriate; Physician withdrawal due to unblinding requires additional discussion.

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Completed By:	Kristin M. Zaterka-Baxter Monitor	09/15/09 Date
Approved By:	_____ NICHD Program Office Signature	_____ Date

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Comments and Key - SUPPORT MRI
Date: Monday, September 14, 2009 9:47:17 AM
Attachments: Comments_Issues MRI 0908_2009.docx
SUPPORT_MRI_Key_REV_090809.DOC

Hi Rose

I forgot to cc you on this when I sent to Kris. Basically just getting all our ducks in a row for data entry for SUPPORT MRIs. I sent off a batch of completed MRI's to Kris on Friday - but the reading process is SLOW going! I see many 6 am readings in my future stretching out for months to come...

Susan

> Date: Sun, 13 Sep 2009 22:09:01 -0700
> To: zaterka
> From: Susan Hintz <srhintz@stanford.edu>
> Subject: Comments and Key - SUPPORT MRI
> Cc: pbarnes-stanford.edu
> Bcc:
> X-Attachments: :Macintosh HD:6525217:Comments_Issues MRI#639120.docx:
> :Macintosh HD:6525217:SUPPORT_MRI_Key_REV_090809.DOC:
>
> Hi Kris and Pat,
>
> Attached are the COMMENTS_ISSUES document (Pat we have talked about these changes and issues, but I have embedded a few additional questions for you - of course we will be seeing each other in early AM hours this week so we can go over it then if you want), and the revised KEY.
>
> Kris, I am sorry this took me a while! You are very patient. As you can see, it is the great American novel (or at least a short story), but I am very sure that I have not made myself too clear in parts. However, you are amazing and a mind reader, so you may understand my ramblings. Please call or email if you are scratching your head, and also if you have questions about MY questions to you!
>
> THANK YOU!!!
>
> Susan
>
> --
>
> Susan R. Hintz, M.D., M.S. Epi
> Associate Professor of Pediatrics
> Division of Neonatal and Developmental Medicine

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SUPPORT Neuroimaging:
COMMENTS/CLARIFICATIONS on MRI central reader FORM/KEY (SRH) *September 8, 2009*

These comments/corrections will follow the order of the MRI03 form as closely as possible, and are based on findings from multiple readings with Dr. Barnes. **These comments also incorporate previous comments from the June 29th reading.**

Note that the yellow highlighted are changes/corrections made to the key in June (sent previously, reiterated here); those in **blue font** are changes/corrections/additions made after the last 2 weeks of reading; and in [redacted] are comments/questions to Kris Zaterka. I have also inserted comments using "Track Changes" for Dr. Barnes.

1) **SECTION A (HEADER):**
   a. A. 5-13 (sequences and views)
      i. If a sequence is NOT circled "Yes", then it means "No" = those images are NOT present.
         1. For instance: If NOTHING is circled under coronal images on any line 5-9, then NO coronal images are present on the MRI
         2. If I am there with Dr. Barnes, I will do my best to circle the "no", but if Dr. Barnes is reading without me, it will likely NOT be circled.
         3. Clarification on sequences evaluated for Signal Abnormalities:
            a. If SPGR or "Ax-Flash" is available, that sequence may be reviewed as the preferred T1 sequence. This sequence may be more sensitive than "traditional" T1, and it is performed increasingly frequently in recent years.
   b. A. 14 (OTHER)
      i. Any other sequences obtained will be noted here. There are a few specific issues that have come up regarding sequences obtained from some of the sites that will be noted here:
         1. "T2=SSFSE": This means that the T2 sequence obtained was actually a single shot fast spin echo (SSFSE). T2 will still be circled YES, but the SSFSE will mean that Dr. Barnes cannot make a determination as to myelination by T2 (C.2.a) and it will be marked "not evaluable" in that section.
         2. "Proton Density" – Center 16 seems to get these a lot, at least early on (pre-2008)
2) **SECTION B (SIGNAL ABNORMALITIES):**
   a. **REGION, SITE**
      i. EPENDYMAL sub-site code: Under "Cerebral", there is now the addition of "ependymal" under each SITE (see yellow highlighted).

REGION	***CODE***	***SITE***		***CODE***
CEREBRAL	C	Frontal	cortical	FC
			subcortical	FSC

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			periventricular	FPV
			ependymal	**FEP**
		Temporal	cortical	TC
			subcortical	TSC
			periventricular	TPV
			ependymal	**TEP**
		Parietal	cortical	PC
			subcortical	PSC
			periventricular	PPV
			ependymal	**PEP**
		Occipital	cortical	OC
			subcortical	OSC
			periventricular	OPV
			ependymal	**OEP**

1. **EPENDYMAL** lesions should NOT be coded GM or WM – they should be left blank (or with line through the GM/WM cell associated with that lesion). If Dr. Barnes thinks a lesion is definitely a WM or GM lesion, **they should be coded differently in terms of site and sub-site** (i.e., as periventricular, cortical, etc).
    a. **Therefore, if a lesion is coded as EPENDYMAL sub-site and GM or WM is coded, this should be flagged.**
2. **EPENDYMAL** lesions will most likely be coded as TYPE = hemorrhagic or mineralization (HEM/MIN). These are likely to represent subependymal hemorrhage or previous IVH in evolution.
3. A new code (see below) has been added for FOCAL/DIFFUSE cell which is **multifocal linear (MFL)**. This code will almost exclusively be used in conjunction with **EPENDYMAL** lesions, will be associated with multiple sub-sites (i.e., FEP, TEP, PEP, OEP), and will be TYPE=HEM/MIN. These lesions are basically mineralization or resolving hemorrhage lining the ependyma around multiple regions around the ventricle. Again, they probably represent subependymal hemorrhage or previous IVH in evolution.

[redacted]

b. SIDE

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i. If I am with Dr. Barnes, I try my best to code lesions as separate lesions, even if similar lesions appear on R and L (i.e., same lesion description for R and L side, entered as lesion #1 and lesion #2). However, if Dr. Barnes is reading without me, he may use his shorthand (as with the Hypothermia MRIs) and write R/L in the SIDE cell associated with the lesion. This will mean that the lesion described is on the RIGHT and LEFT side (i.e., two lesions).

c. **T1, T2, FL, GRE, DWI, ADC**
   i. If the cell is left **blank**, it means it cannot be seen on that sequence = ISOINTENSE or I.
      1. [redacted]
   ii. However, NOTE that the cell may be left blank also if that sequence was NOT DONE! So, the programmers/data entry folks should know that they shouldn't just replace a blank cell with "I" code. [redacted]
   iii. Note that I have removed the line in the KEY that says "If lesion no seen on sequence, code "98" or if sequence not done, code"99".

d. **Focal/Diffuse**
   i. As noted above a new code needs to be added for FOCAL/DIFFUSE cell which is **multifocal linear (MFL)**. This code will almost exclusively be used in conjunction with **EPENDYMAL** lesions, will be associated with multiple sub-sites (i.e., FEP, TEP, PEP, OEP).
   ii. FP = focal punctate. The lesion is 1 mm or less in diameter
   iii. FL = focal linear.
   iv. FN = focal nodular
   v. D = diffuse. [I doubt this will be used too much. It is very hard to QUANTITATE a diffuse lesion.]
   vi. MF = multifocal nodular. Multiple scattered nodular lesions.

e. **GM/WM**
   i. When I am with Dr. Barnes during the reading, I am trying to be AS CLEAR as possible about whether a lesion is GM or WM – if there are lesions in both GM and WM, I do my best to make sure to mark them separately. However, if Dr. Barnes is reading alone, **he may mark GM/WM and it means that both WM and GM are involved in the area of injury**.
   ii. If the lesion cannot be classified as EITHER WM or GM, it should be left blank or with a line through that cell. This should really only occur with a limited number of sites –
      1. EPENDYMAL lesions as described above,
      2. VENT lesions

Comment [SH1]: PAT: Do you agree with this? For instance, I find the whole "DEHSI" issue a bit difficult to sort out unless all imaging is done in the same place with exactly the same protocol

Comment [SH2]: PAT: Please review this section of comments pertaining to GM/WM column of the Signal Abnormalities section of the form. Is this all correct from your perspective?

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3. *There may be others, but I can't think of any at the moment!*

f. **SIZE**
   i. Size will be entered in millimeters (i.e., 3 = 3 mm).
   ii. For FP, 1 will be entered. (See section d above).
   iii. If the lesion is FN, the diameter of will be entered. If multifocal nodular (MF), the diameter of the largest lesion will be entered. If focal linear, this will mean that the diameter is 1 mm or less and the LENGTH of the lesion will be entered. **For MFL, the SIZE CELL will be left blank** because MFL will mean the lesion spans over several sub-site areas. In any case, as noted above, the MFL code will be used probably almost exclusively for the ependymal Hem/Min lesions.

g. **TYPE**
   i. See Key.
   ii. If a lesion is CYSTIC, and it appears to be a porencephalic cyst, **the lesion # should be referenced and this should be noted on page 1 (in the blank space under the signal abnormalities grid) or in the COMMENTS at the end of the form.**
   [redacted]
   iii. NOTE: Some lesions are marked HEM/MIN. It is difficult to know whether it is actually blood or mineralization. This is especially true for those lesions only seen on GRE.
   iv. [redacted]analysis
   v. Also, the HEM/MIN or NCYS lesions that are seen ONLY on GRE (i.e., isointense in all other sequences) may need to be broken out in analysis separately at some point in analysis.

Comment [SH3]: Pat: I would suspect you would agree with this statement and the one following (g.iv). It may not be possible for you to distinguish hemorrhage from mineralization, and in any case, these are near-term infants – the likelihood that there is true active hemorrhage I would think is remote.

3) **SECTION C. MATURATION AND DEVELOPMENT**

a. **C 1. GRAY MATTER**

Dr. Barnes' experience, coupled with the brain MRI's reviewed thus far from this extremely preterm SUPPORT cohort, have revealed a concerning and more delayed than anticipated cortical maturational pattern. This has been noted in previous literature (Inder 2003), with very limited number of extremely preterm patients. Furthermore, previous literature has only recorded only *broad maturation categories of up to 3-5 week PMA* (Woodward 2005, Huppi 1996, Childs 2001) based on the best available developmental data from 1970's and 1980's (Chi 1977, McArdle 1987, Martin 1988). It is therefore likely that the description of the SUPPORT MRI cohort cortical maturational pattern will bring important new information to the literature. It is therefore important to parse the cortical gray matter maturation as carefully as possible.

   i. Therefore, **"G 2.5" and "G 3.5" categories have been added** because the original stages and previous descriptions in the literature were simply too far apart and did not encompass the finer level of detail in maturational changes that have been seen. See revised KEY below.

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***C.1. GRAY MATTER MATURATION* (ref. 1-3, 8-10)**	
Stage	***C.1.a. Cortical maturation markers***
G0	Frontal and occipital cortex completely smooth, insula widely open
G1	Frontal cortex still smooth, but some sulci in occipital cortex
G2	Frontal and occipital cortex with some convolutions, frontal sulci shallow. Internal surface of insula more convoluted.
G 2.5	**All G2 markers, approaching G3 - however, secondary gyri are not present in all areas as noted in G3**
G3	Presence of marginal sulcus and paracentral gyrus. Frontal and occipital cortex folded and richer in sulci. Insula more convoluted and infolded. Secondary gyri present in frontal, superior and middle temporal, pre- and post-rolandic, insula, occipital
G 3.5	**All G3 markers, approaching G4 – secondary gyri of G4 present, but anterior and posterior orbital gyri may not be established**
G4	Secondary gyri present transverse and inferior temporal; Anterior and posterior orbit gyri should be established.
G5	Teritiary inferior temporal and inferior occipital gyri and sulci present. White matter now isointense with gray matter on T1
NE	Not Evaluable

b. C.2.a WHITE MATTER Markers of myelination

i. As noted above (section 1.b.i.1), T2 will be marked Not Evaluable in cases where T2 was obtained by SSFSE

ii. As described in the June 29th changes, clarification as to the myelination pattern was necessary. The revised definition recognizes the need for more detailed white matter maturation pattern based on completeness of PLIC myelination at this postmenstrual age range. This is consistent with the literature. The following has been changed in the key:

***C.2.a. WHITE MATTER MATURATION* (ref 1.3.5)**	
For each hemisphere, mark level of maturation noted on both T1 and T2	
Stage	***C.2.a. Myelination***
W0	Brainstem, cerebellar peduncle, inf. Colliculus, cerebellar vermis
W1	Subthalamic nuclei, globus pallidus, ventrolat thalamus
W2	Part of PLIC (i.e., caudal portion), or very poor myelinatjon of PLIC
W3	Complete or near-complete PLIC
W4	Corona radiata
W5	Corticospinal tracts of the precentral and postcentral gyri
NE	Not Evaluable

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c. **C.2.b WHITE MATTER Corpus Callosum**
   i. Should read "thinning" rather than "enlargement" for column headings "Mild-Moderate enlargement" and Marked enlargement". This has been changed on the key.

d. **C.2.e WHITE MATTER Qualitative assessment of lateral ventricular dilation**
   i. Currently, the form indicates that only one box may be checked per hemisphere – this needs to be changed specifically to allow **SHUNTED** to be checked along with another box for each hemisphere
      1. For instance, there may be a shunt in place in the left

4) **D.3.A - HEMORRHAGE GRADES (Papile classification)**
   a. We are not utilizing the section on Papile classifications (D.3.A)
      i. This is because these MRI's are LATER imaging, Papile classifications are not utilized on the late CUS form, and any intraventricular hemorrhage or echodensity would be identified on the "signal abnormalities" section (B) utilizing the VENT site code.

5) **Need for massive injury code...similar to "hemispheric devastation" assignment in Hypothermia?**
   a. There have been a few cases already in which there is massive (usually bilateral) ventricular dilation, and enormous injury leading to ***"obliteration of sulcation and gyration landmarks, deformation"***. I have been writing these in - using about those words - on the front of the envelope and also in the E. (COMMENTS) section on page 3 of the form. We also write what this severe injury likely represents – in most cases so far, massive bilateral post-hemorrhagic hydrocephalus, in some cases with porencephalic cyst.
   b. If Dr. Barnes judges this to be the case, ***he <u>cannot</u> assign gray matter maturation score (C.1.a), Subarachnoid space measurements or assessments (C.1.b) or myelination score (C.2.a) so those will be left blank. Also, there will be NO cavum septum pellucidum or Sylvian fissure measurements made (see below).*** However, Dr. Barnes is still able to detail signal abnormalities (if any are specifically seen)

6) **ADDITIONAL MEASUREMENTS:**
   a. We will always (except in the case above with "obliteration of landmarks) be measuring the following - **cavum septum pellucidum (CSP), Sylvian fissure Left (L) and Right (R).** (Sylvian fissure may be abbreviated also to SF)
      i. When I am reading with Dr. Barnes, I always record these measurements in E. Other, "COMMENTS" at the end of page 3. However, if Dr. Barnes reads alone, he may record them in blank spot at the end of page 2 (but he is trying to break this habit).

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ii. Similar to the case with additions to the CUS central reading form after the first central reading (May 10-11), we would therefore like specific data fields to be created for these measurements. I have added the following to the KEY under section E. Other:
    1. Cavum septum pellucidum (CSP)
        a. "Cavum septum pellucidum: measure CSP size in millimeters on axial image. If no CSP is seen, record 0"
    2. Sylvian fissure
        a. "Record Left (L) and Right (R) Sylvian fissure size in millimeters on maximum AP dimension on axial imaging"

7) "Qualitative assessments"

a. This study will be the first to make such complete and detailed measurements. Previous studies have infrequently reported measurements associated with enlargement or thinning of specific brain features. For instance, there are extremely limited data on the actual expected measured thickness of the corpus callosum at term, much less that seen in preterm infants at term equivalent age.
b. For the purposes of our scoring sheet, qualitative assessments are meant to be just that – qualitative. We have some guidelines as seen in the key, but these qualitative assessments are not necessarily based on measurements, but rather are meant to reflect the clinical impression of an experienced neuroradiologists. This would be similar to a clinical reading.
    i. The "qualitative assessment" may be evaluated on any image or group of images. For instance, the corpus callosum "qualitative" assessment may be evaluated on axial and sagittal images; ventricular dilation may be evaluated on axial and coronal images; etc..

8) Expanded reference list:

a. The reference list has been expanded as follows for completeness, and included in the Key

1. Huppi P, et. al. Peds Res 1996;39:895-901
2. Inder T, et. al. J Pediatr 2003;143:171-179
3. Childs A-M, et. al. AJNR 2001;22:1577-1582
4. Valkama AM, et. al. Acta Paediatr 2000;89:348-355
5. Counsell S, et. al. AJNR 2002;23:872-881
6. Poland RL, Slovis TL, Shankaran S. Pediatr Radiol 1985;15:12-14
7. Miller SP,et. al. AJNR 2003; 24:1661-1669
8. McArdle CB, et. al. Radiology 1987; 162:223-229

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9. Chi JG, et. al. Ann Neurol 1977; 1:86-93
10.Martin E, et. al. J Comp Assist Tomog 1988; 12:917-922
11. Woodward L, et. al. NEJM 2006; 355:685-699 and Suppl material

The following pertain to the SUPPLEMENTAL FORM:

1) EVALUTING WHITE MATTER LESIONS FOR SUMMARY CLASSIFICATIONS: White matter lesions will be "counted" for both summary classification systems if a signal abnormality is seen on any sequence and judged by Dr. Barnes to represent a true white matter lesion. In other words, not only the T1 and T2 weighted images will be evaluated for these scores.
2) B.1. Miller Classification
    a. Note that there are 2 typos in the line following "Moderate". See below in red is corrected – the less than and greater than signs got turned around in the forms

Moderate	3 or more areas of T1 signal abnormality or these areas measuring **>2 mm but <5% of** hemisphere involved

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SUPPORT Neuroimaging and Outcomes: CENTRAL MRI KEY ***Rev. SRH yellow=6/29/09, blue=9/8/09***

B. SIGNAL ABNORMALITIES

REGION	CODE	SITE		CODE
CEREBRAL	C	Frontal	cortical	FC
			subcortical	FSC
			periventricular	FPV
			ependymal	FEP
		Temporal	cortical	TC
			subcortical	TSC
			periventricular	TPV
			ependymal	TEP
		Parietal	cortical	PC
			subcortical	PSC
			periventricular	PPV
			ependymal	PEP
		Occipital	cortical	OC
			subcortical	OSC
			periventricular	OPV
			ependymal	OEP
		Parasagittal area		PARA
		Perirolandic		PER
		Perisylvian***		PERI
		Insular***		INS
INTRAVENTRIC***	VENT			
CEREBELLAR***	BEL	Vermian		V
		Hemispheric		H
BASAL GANGLIA***	BG	Putamen		P
		Caudate		CAU
		Globus Pallidus; Lentiform nucleus		GP
THALAMUS***	T			
INTERNAL CAPSULE				
Poster Limb***	PLIC			
Anterior Limb***	ALIC			
CORONA RADIATA***	CR			
HIPPOCAMPUS***	HIP			
BRAINSTEM	BS	Medulla		
			Ventral	MVen
			Dorsal	MDor
		Pons		
			Ventral	PVen
			Dorsal	PDor
BRAINSTEM (cont)				
		Midbrain		
			Ventral	MidVen
			Dorsal	MidDor
CORPUS CALLOSUM	CC	Genu		G
		Body		B
		Splenium		SPL
PITUITARY	PIT			
HYPOTHALAMUS	HY			
OPTIC CHIASM	OP			
EXTRA-AXIAL***	EX	Subarachnoid		SAR
		Subdural		SDR
		Epidural		EPI
VASCULAR	VAS	Arterial		ART
		Venous		VEN
OTHER	OTH			

SIDE	CODE
Right	R
Left	L

T1, T2, IR, FL, GRE, DWI, ADC

INTENSITY	CODE
Hypointense/Low	L
Isointense	I
Hyperintense	H

FOCAL/DIFFUSE	CODE
If focal code	
Punctate	FP = 1 mm or less in diameter
Linear	FL
Nodular	FN
If diffuse	D
If multifocal	MF or MFL (multifocal linear)

GM/WM	CODE
If gray matter	GM
If white matter	WM

SIZE: **Enter MEASURED diameter of lesion, i.e., 3 = 3mm, 4 = 4mm, etc. If multifocal, enter largest diameter. If linear, enter measured LENGTH of lesion.**

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TYPE	***CODE***
Cystic	CYS **If PORENCEPHALIC cyst, note lesion # and make comment on page 1, or page 3 in Section E.**
Non-Cystic	NCYS
Hemorrhage	HEM
Mineralization	MIN
Infarct	INF
Gliosis	GLI

TYPE	***GUIDELINES for Interpretation*** (Based on previous literature incl. ref #7)
Cystic/cavitation abnormalities	T1 hypo T2 hyper, FL hypo
Non-Cystic abnormalities	T1 hyper or hypo T2 hyper FL hyper ***Note; T1 hyper in absence of marked T2 hypo is likely gliosis*
Hemorrhage or mineralization	GRE hypo +/- T1 hyper and MARKED T2 hypo

C. MATURATION AND DEVELOPMENT

C.1. GRAY MATTER MATURATION **(ref. 1-3, 8-10)**

Stage	***C.1.a. Cortical maturation markers***
G0	Frontal and occipital cortex completely smooth, insula widely open
G1	Frontal cortex still smooth, but some sulci in occipital cortex
G2	Frontal and occipital cortex with some convolutions, frontal sulci shallow. Internal surface of insula more convoluted.
G 2.5	All G2 markers, approaching G3 - however, secondary gyri are not present in all areas as noted in G3
G3	Presence of marginal sulcus and paracentral gyrus. Frontal and occipital cortex folded and richer in sulci. Insula more convoluted and infolded. Secondary gyri present in frontal, superior and middle temporal, pre- and post-rolandic, insula, occipital
G 3.5	All G3 markers, approaching G4 – secondary gyri of G4 present, but anterior and posterior orbital gyri may not be established
G4	Secondary gyri present transverse and inferior temporal; Anterior and posterior orbit gyri should be established.
G5	Teritiary inferior temporal and inferior occipital gyri and sulci present. White matter now isointense with gray matter on T1
NE	Not Evaluable

C.1.b. Subarachnoid Space For each hemisphere, mark as described

Record widest measure at ant./post. IHF, lat. post. parietal SAS at centrum semiovale. The following may serve as guidelines for severity of enlargement

Normal	<4 mm; or "small space, barely visible" (ref #11)
Mild-moderate enlargement	4-6 mm; or "mildly enlarged CSF space with visible enlarge of interhem and extracereb space" (ref #11)
Marked enlargement	>6 mm; or "more substantially enlarged, visible space between gyri and interhem and extracereb" (ref #11)

Stage	***C.2.a. Myelination***
W0	Brainstem, cerebellar peduncle, inf. colliculus, cerebellar vermis
W1	Subthalamic nuclei, globus pallidus, ventrolat thalamus
W2	Part of PLIC (i.e., caudal portion), or very poor myelination of PLIC
W3	Complete or near-complete PLIC
W4	Corona radiata
W5	Corticospinal tracts of the precentral and postcentral gyri
NE	Not Evaluable

C.2.b and c Corpus Callosum Thinning Qualitative Summary Question

NOTE: These are *qualitative assessments*; quantitative measures will be primary

C.2.d. Lateral ventricle measurements

Measure diameter ventricular and brain region as indicated in millimeters for both left and right. ***NOTE:*** V/B ratio can be calculated from these measures by data center after submission of completed form

C.2.e. Qualitative assessment of lateral ventricle dilation (ref 4,6,7)

Guidelines from the literature include the following:

"Mild": abnormal, with V/B ratio ~1/3; "moderate": V/B ratio 1/3-2/3; "severe": V/B ratio>2/3 (measured at level of atria on coronal)

Mild ventriculomegaly": largest ventricular diameter at level of glomus of the choroid = 8-10 mm; "Moderate-severe": >10 mm (ref. 7)

Frontal horn, midbody	V/B ratio>0.35* = "abnormal"
Trigone	V/B ratio >0.60 = "abnormal

C.2.f. Third, Fourth Ventricle, temporal and occipital horn

Measure indicated region in mm. Then assess qualitatively as described

E. OTHER: Report structural abnormalities and describe in comments

The following measurements will also be recorded in COMMENTS area:

Sylvian fissures: Record L and R Sylvian fissure size in millimeters on maximum AP dimension on axial imaging

Cavum Septum Pellucidum (CSP): Record CSP in millimeters on axial imaging. If no CSP is seen, record 0.

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References:

1. Huppi P, et. al. Peds Res 1996;39:895-901
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3. Childs A-M, et. al. AJNR 2001;22:1577-1582
4. Valkama AM, et. al. Acta Paediatr 2000;89:348-355
5. Counsell S, et. al. AJNR 2002;23:872-881
6. Poland RL, Slovis TL, Shankaran S. Pediatr Radiol 1985;15:12-14
7. Miller SP,et. al. AJNR 2003; 24:1661-1669
8. McArdle CB, et. al. Radiology 1987; 162:223-229
9. Chi JG, et. al. Ann Neurol 1977; 1:86-93
10. Martin E, et. al. J Comp Assist Tomog 1988; 12:917-922
11. Woodward L, et. al. NEJM 2006; 355:685-699 and Suppl material

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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Sunday, September 13, 2009 7:41:32 AM

Yes

From: "Higgins, Rosemary (NIH/NICHD) [E]" [higginsr@mail.nih.gov]
Sent: 09/11/2009 07:39 AM AST
To: " (Luc.Brion@UTSouthwestern.edu)" <Luc.Brion@UTSouthwestern.edu>; " (rohls@unm.edu)" <rohls@unm.edu>; "aaf2@po.cwru.edu" <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; "alaptook@WIHRI.org" <alaptook@WIHRI.org>; "Ambal (ambal@uab.edu)" <ambal@uab.edu>; "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; Michael Cotten; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>; "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>; Michelle Walsh <mcw3@po.cwru.edu>; MIckey Caplan <mca113@Northwestern.edu>; "Oh William (E-mail)" <william_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald Goldberg; Seetha Shankaran <sshankar@med.wayne.edu>; "Stevenson David (E-mail)" <dstevenson@stanford.edu>; "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>; "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>; "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>
Cc: Neil Finer <nfiner@ucsd.edu>; "'Duara, Shahnaz'" <SDuara@med.miami.edu>; "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>; "Zaterka-Baxter, Kristin" <kzaterka@rti.org>
Subject: SUPPORT Protocol and forms

As you may recall, Ed Bell had requested to share the SUPPORT protocol and forms with Ophthalmology colleagues to develop a secondary analysis of the SUPPORT trial data to look at growth and development of ROP. I have discussed with Drs. Finer and Duara who are ok with this provided the primary analyses and the secondary growth analyses are first done. **Send me a yes/no vote to share the forms with Ed's colleagues by September 15.**

Thanks
Rose

Rosemary D. Higgins, MD
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol and forms
Date: Sunday, September 13, 2009 7:05:15 PM

I am OK with this
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 11, 2009 4:40 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Finer, Neil; 'Duara, Shahnaz'; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: SUPPORT Protocol and forms

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Thanks
Rose

Rosemary D. Higgins, MD
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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Luc Brion
Subject: Re: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 10:52:52 PM

---

yes--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 9/11/09 6:39 AM >>>
As you may recall, Ed Bell had requested to share the SUPPORT protocol and forms with Ophthalmology colleagues to develop a secondary analysis of the SUPPORT trial data to look at growth and development of ROP. I have discussed with Drs. Finer and Duara who are ok with this provided the primary analyses and the secondary growth analyses are first done. Send me a yes/no vote to share the forms with Ed's colleagues by September 15.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 6:20:38 PM

AOK to share with Ed Bell's colleagues

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

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From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik
Cc: StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Webb, Robin E.; Cunningham, Meg; Zaterka-Baxter, Kristin
Subject: SUPPORT Call
Date: Friday, September 11, 2009 12:28:58 PM

The call to discuss SUPPORT has been scheduled for:

Monday 9/28
2:00pm ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310-(b) (6)

Then, enter Participant Passcode:
(b) (6)

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

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From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 11:38:36 AM

Yes.
Krisa

>As you may recall, Ed Bell had requested to share the SUPPORT
>protocol and forms with Ophthalmology colleagues to develop a
>secondary analysis of the SUPPORT trial data to look at growth and
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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 10:02:50 AM

Yes, with a great deal of concern for the process
And compromise of the main trial and pre planned secondaries.
New secondaries, particularly that growth rates could substitute for known
Risk factors for ROP which is speculative at best, should only occur after
The preplanned secondary studies.

Michele Walsh
beeper(b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 11, 2009 7:40 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Neil Finer; 'Duara, Shahnaz'; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: SUPPORT Protocol and forms

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Thanks
Rose

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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 9:28:02 AM

Hi Rose, Yes from Cincinnati. Thanks, Kurt

On 9/11/09 7:39 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> As you may recall, Ed Bell had requested to share the SUPPORT protocol and forms with Ophthalmology colleagues to develop a secondary analysis of the SUPPORT trial data to look at growth and development of ROP. I have discussed with Drs. Finer and Duara who are ok with this provided the primary analyses and the secondary growth analyses are first done. **Send me a yes/no vote to share the forms with Ed's colleagues by September 15.**
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
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> higginsr@mail.nih.gov

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 8:39:56 AM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 11, 2009 7:40 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Wallace, Dennis; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole, W. Kenneth; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Neil Finer; 'Duara, Shahnaz'; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: SUPPORT Protocol and forms

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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 8:36:45 AM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 11, 2009 7:40 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Neil Finer; 'Duara, Shahnaz'; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: SUPPORT Protocol and forms

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 7:59:50 AM

yes

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 11, 2009 6:40 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol and forms
Date: Friday, September 11, 2009 7:45:23 AM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E]
To: (Luc.Brion@UTSouthwestern.edu) ; (rohls@unm.edu) ; aaf2@po.cwru.edu ; Abhik Das ; alaptook@WIHRI.org ; Ambal (ambal@uab.edu) ; Brad Yoder (Bradley.yoder@hsc.utah.edu) ; Brenda Poindexter ; Carlo Waldemar (E-mail) ; cotte010@mc.duke.edu ; Dennis Wallace ; Ed Bell ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Ivan Frantz (ifrantz@tuftsmedicalcenter.org) ; Kennedy, Kathleen A; Kristi Watterberg ; Kurt Schibler [kurt.schibler@cchmc.org] ; Michelle Walsh ; MIckey Caplan ; Oh William (E-mail) ; Pablo Sanchez ; Poole Kenneth (E-mail) ; Roger Faix ; Ronald GOldberg ; Seetha Shankaran ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson, Jon E; VanMeurs, Krisa
Cc: Neil Finer ; 'Duara, Shahnaz' ; Archer, Stephanie (NIH/NICHD) [E] ; Zaterka-Baxter, Kristin
Sent: Fri Sep 11 06:39:45 2009
Subject: SUPPORT Protocol and forms

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Cc: Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Hot Topics 2010
Date: Wednesday, September 09, 2009 7:02:57 PM

YES! I think it will be great to share our data with so many neonatologists.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
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Birmingham, AL 35233-7335
Phone: 205 934 4680
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Sent: Wednesday, September 09, 2009 9:50 AM
To: Neil Finer; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics 2010

Hi,

Jerry Lucey would like a presentation from the SUPPORT study in **2010** at Hot Topics – **NOT THIS YEAR, BUT NEXT YEAR.**

The current plan is to have the first two papers written and submitted in the near future, probable abstracts at PAS and presentation at American Thoracic Society 2010 (May) if accepted.

Neil and Wally are ok with this.

Please send me a yes/no vote for presentation by September 11.

Thanks
Rose

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics 2010
Date: Wednesday, September 09, 2009 12:38:25 PM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wed 9/9/2009 10:49 AM
To: Neil Finer; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics 2010

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Duke
Date: Wednesday, September 09, 2009 12:22:44 PM

Rose:

Please see below for small suggested changes. I also got the sense from Kris that Duke may be doing a lot of other industry funded studies, with the result that NRN studies are getting lower priority/attention. However, that may be something you enquire about when you are there, rather than putting it in this email. Incidentally, late September is not good for me (Study Section, among other things), but you may not need me there, and I could see if Dennis can make it.

As you may know, Kris is (b) (6) and you may not hear back from her right away.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 09, 2009 11:30 AM
To: Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Das, Abhik
Subject: Duke
Importance: High

Carolyn, Kris and Abhik – I want to send this to Ron today: please edit!!!

The staff at RTI have briefly updated me on last week's visit to Duke. There are several issues which need to be addressed in person. I can come to Duke on 9/29 – will that work for you and the site? It is imperative that I visit in the next few weeks.

The following outstanding items are of urgent importance:

1. SUPPORT primary outcome data including death, BPD and ROP for each of the 64 infants enrolled at Duke needs to be formally approved by you or Mike Cotten (as alternate PI). This is time sensitive and needs to be done by the end of the month as the investigators are anxious to have a final data set.
2. Primary source data need to be available in the patient's chart. Apparently, ophthalmology exams from the primary source, or copies thereof, are not readily available, which makes it impossible to properly audit these data. ~~There is difficulty in obtaining eye exams from the primary source.~~
3. IRB approval process has several levels of review. We would like an efficient system for NRN studies.
4. Collaborative organization of the team at the Duke site that would enable more efficient running of NRN studies.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine

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Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Walid.Salhab@SBCglobal.net; Luc Brion
Subject: Re: Hot Topics 2010
Date: Wednesday, September 09, 2009 12:00:01 PM

Yes-but like you stated, next year after pas,etc-pablo
-----Original Message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: Oh William (E-mail) <william_oh@brown.edu>
To: Ed Donovan <edward.donovan@cchmc.org>
To: Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>
To: Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>
To: Roger Faix <Roger.Faix@hsc.utah.edu>
To: Brenda Poindexter <bpoindex@iupui.edu>
To: Krisa VanMeurs <vanmeurs@leland.stanford.edu>
Cc: Stephanie (NIH/NICHD) [E] Archer <archerst@mail.nih.gov>
To: cotte010@mc.duke.edu <cotte010@mc.duke.edu>
To: Ronald GOldberg <goldb008@mc.duke.edu>
To: Seetha Shankaran <sshankar@med.wayne.edu>
To: MIckey Caplan <mca113@Northwestern.edu>
To: Stoll Barbara(E-mail) <barbara_stoll@oz.ped.emory.edu>
To: CarloWaldemar (E-mail) <wcarlo@peds.uab.edu>
To: aaf2@po.cwru.edu <aaf2@po.cwru.edu>
To: Michelle Walsh <mcw3@po.cwru.edu>
To: Abhik Das <adas@rti.org>
To: Dennis Wallace <dwallace@rti.org>
Cc: Kristin Zaterka-Baxter <kzaterka@rti.org>
Cc: Meg' 'Cunningham <mcunningham@rti.org>
Cc: Carolyn Petrie' 'Huitema <petrie@rti.org>
To: Poole Kenneth (E-mail) <poo@rti.org>
To: Kristi Watterberg <kwatterberg@salud.unm.edu>
To: Stevenson David (E-mail) <dstevenson@stanford.edu>
To: Ivan Frantz(ifrantz@tuftsmedicalcenter.org) <ifrantz@tuftsmedicalcenter.org>
To: Ambal (ambal@uab.edu) <ambal@uab.edu>
To: Neil Finer <nfiner@ucsd.edu>
To: Ed Bell <Edward-bell@uiowa.edu>
To: (rohls@unm.edu) <rohls@unm.edu>
To: Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>
To: Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>
To: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>

Sent: 9/9/2009 9:49:53 AM
Subject: Hot Topics 2010

Hi,
Jerry Lucey would like a presentation from the SUPPORT study in 2010 at Hot Topics - NOT THIS YEAR, BUT NEXT YEAR.

The current plan is to have the first two papers written and submitted in the near future, probable abstracts at PAS and presentation at American Thoracic Society 2010 (May) if accepted.

Neil and Wally are ok with this.

Please send me a yes/no vote for presentation by September 11.

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Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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higginsr@mail.nih.gov

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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Hot Topics 2010
Date: Wednesday, September 09, 2009 11:42:57 AM

Rose, My vote is yes. Kurt

On 9/9/09 10:49 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
> Jerry Lucey would like a presentation from the SUPPORT study in **2010**
> at Hot Topics – **NOT THIS YEAR, BUT NEXT YEAR.**
>
> The current plan is to have the first two papers written and submitted in the near future, probable abstracts at PAS and presentation at American Thoracic Society 2010 (May) if accepted.
>
> Neil and Wally are ok with this.
>
> Please send me a yes/no vote for presentation by September 11.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
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> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

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From: Fanaroff, Avroy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics 2010
Date: Wednesday, September 09, 2009 11:22:44 AM

Yes
Av

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wed 9/9/2009 10:49 AM
To: Neil Finer; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics 2010

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Thanks
Rose

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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics 2010
Date: Wednesday, September 09, 2009 11:21:45 AM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 09, 2009 10:50 AM
To: Neil Finer; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics 2010

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Neil and Wally are ok with this.

Please send me a yes/no vote for presentation by September 11.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics 2010
Date: Wednesday, September 09, 2009 10:51:43 AM

Yes, assuming the study has successfully undergone peer-review (by any of the below plans – manuscript acceptance, presentation at PAS or ATS)
Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 09, 2009 10:50 AM
To: Neil Finer; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Poindexter, Brenda B; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics 2010

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Thanks
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D.
To: Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT data!
Date: Tuesday, September 08, 2009 6:51:13 PM

There is an absolute risk diff (NS)for phys def BPD of 3% favoring the low sat group but there are several biases including that the physiologic test not used if FiO2 is >30% (so less babies in the higher sat group would have an attempt to be weaned off with the phys def test) and that clinicians may be more likely to go back on O2 during the testing if baseline FiO2 is higher before the testing. Thus, this ARR is likely an over-estimation of the truth. With such a large sample size, I think the best interpretation is that there is not a large benefit of low sats targeting for the reduction of BPD.

What do you think of these thoughts?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 08, 2009 2:20 PM
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT data!

Nor I – The target sat for the room air definition is that you are in range – if in room air almost all of our infants are using standard oximeters by this time anyway. I doubt that this is a factor – even if I understood it.

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, September 08, 2009 11:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: RE: SUPPORT data!

I am not sure I understand her conjecture completely.

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 08, 2009 2:04 PM
To: Das, Abhik
Subject: FW: SUPPORT datal

Can you answer?

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, September 04, 2009 10:51 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: SUPPORT datal

Dear Rose,
I wondered if the significant effect on BPD outcome is a matter of higher oxygen sat group "needing" oxygen to reach that target sat-or something else? The physiologic BPD was no different between groups.--Carol

Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, August 24, 2009 12:51 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Fw: SUPPORT call

Hi
Here is a first look at the data - please keep confidnetial!!!
Thanks for all your help!!!
Rose

Rosemary D. Higgins, MD
Program Scientist

From: Finer, Neil <nfiner@ucsd.edu>
To: Finer, Neil <nfiner@ucsd.edu>; 'Cunningham, Meg' <mcunningham@rti.org>; 'alaptook@WIHRI.org' <alaptook@WIHRI.org>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik' <adas@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; 'kurt.schibler@cchmc.org' <kurt.schibler@cchmc.org>; 'mcw3@cwru.edu' <mcw3@cwru.edu>; 'nancy newman' <nxs5@case.edu>; 'Roger.Faix@hsc.utah.edu' <Roger.Faix@hsc.utah.edu>; 'Wallace, Dennis' <dwallace@rti.org>; 'Wally Carlo, M.D.' <WCarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Cc: 'Newman, Jamie' <newman@rti.org>; 'sharon.gough@hsc.utah.edu' <sharon.gough@hsc.utah.edu>; Archer, Stephanie (NIH/NICHD) [E]; 'Brenda Vecchio' <BVecchio@WIHRI.org>; Martinez, Fernando <fmartinez@ucsd.edu>; 'Huitema, Carolyn Petrie' <petrie@rti.org>; 'msumner@peds.uab.edu' <msumner@peds.uab.edu>; 'Zaterka-Baxter, Kristin' <kzaterka@rti.org>; 'Starlett Williams' <StWilliams@peds.uab.edu>; 'Irene, Amanda' <airene@rti.org>
Sent: Mon Aug 24 12:21:49 2009
Subject: RE: SUPPORT call

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Hello Everyone
I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik.
Please find the basic demographic tables and the outcome of BPD and death etc. You will note that Death/BPD using the need for oxygen at 36 weeks as the postulated primary – because that was the data we based the study on – is significant both unadjusted and adjusted. Note that BPD is also less for the Low SpO2 group – but for that study, we need ROP which we are still waiting for.
Congratulations on a study well done to you all and the coordinators, and RTI
Wally Wade and I will be at RTI a week today to review all the data and I have already started the first paper.
Be well
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Finer, Neil
Sent: Tuesday, August 11, 2009 7:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Here are the Tables we sent to Marie

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

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From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

Tuesday, 8/11
11:00am ET

Dial:
Within the USA
866-675-(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From: Duara, Shahnaz
To: "Finer, Neil"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondary
Date: Tuesday, September 08, 2009 5:16:02 PM

Fine – that sounds reasonable.
Shahnaz

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 08, 2009 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz
Subject: RE: SUPPORT secondary

I agree.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 08, 2009 10:28 AM
To: 'Duara, Shahnaz'; Finer, Neil
Subject: RE: SUPPORT secondary

They could submit the proposal, but not get any look at the data until you are finished

Rose

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, September 08, 2009 1:25 PM
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT secondary

Neil,
What do you think? I would hate to have the data picked clean before we even get a chance to look at it. Boundaries are hard to establish once a sub-analysis gets underway.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 08, 2009 12:42 PM
To: Duara, Shahnaz; Finer, Neil
Cc: Das, Abhik
Subject: FW: SUPPORT secondary

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Ed would like to submit a proposal – should I ask him to send it?
Thanks
Rose

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, September 08, 2009 10:51 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondary

Does that mean we can't submit the new proposal until the main trial is in press?
Ed

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 08, 2009 8:55 AM
To: Bell, Edward
Subject: FW: SUPPORT secondary

See response from Shahnaz

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Thursday, August 27, 2009 5:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondary

Rose,
Sorry – just back from India. I understood from most of the discussion around this that there was concern about data use before we publish our main findings. I would prefer to wait until we publish our main findings before we share findings outside the study.
Again, sorry for the delay.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 25, 2009 12:53 PM
To: Duara, Shahnaz
Subject: SUPPORT secondary

Shahnaz – I had sent this to you while you were away – Neil wanted your input – can you let me know what you think?
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 10, 2009 11:03 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]; 'Finer, Neil'; Duara,

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Shahnaz; Navarrete, Cristina
Subject: Request for collaborative proposal

Based on a recent publication Löfqvist et al from Lund (Arch Ophthalmol 2009; 127:622), Ed Bell is interested in collaborating with Drs. Binebaum and Quinn from CHOP Ophthalmology to evaluate growth rates and evolution/resolution of ROP. Please send a yes/no vote by August 17 to share the SUPPORT main trial protocol/forms as well as the growth secondary protocol/forms with the folks from CHOP.

Rosemary D. Higgins, MD
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From: Zaterka-Baxter, Kristin
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Cross-form queries for SUPPORT infants
Date: Tuesday, September 08, 2009 9:00:13 AM
Attachments: Cross-form queries 04SEP09.doc
Cross-form queries 04SEP09.zip

Would you like me to send these queries out or Rose, would you prefer they come from you; please just let me know, I am happy to send.
Thanks,
Kris

From: Gantz, Marie
Sent: Saturday, September 05, 2009 12:06 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Rich, Wade'
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Cross-form queries for SUPPORT infants

Attached is a zip file containing documents with cross-form queries (GDB and SUPPORT forms) for SUPPORT infants. A summary of the queries is also attached. These queries impact some of the secondary outcomes for the SUPPORT papers, so hopefully the centers will be able to clear them up quickly. As before, if they can make a note of how the query was resolved and return the query document to us with those notes it will help us track their progress. I will be out of town for the next two weeks, but hopefully the centers will be able to resolve most of the queries by the time I return on September 21.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Secondary cross-form queries (may be >1 per infant)

The FREQ Procedure

Query			
queryNum	Frequency	Cumulative Frequency
Birth date was >120 days ago but SUPP09 has not been completed	8	8
Infant was outborn per NG02 but was enrolled in SUPP01	2	10
NG02 birth time does not match SUPP03 delivery time	55	65
NG02 birth date/time is after SUPP04 NICU admission time	3	68
Per SUPP03 status following resuscitation was death but per SUPP04 infant was admitted to NICU	1	69
NG03e death date/time is before NG02 birth date/time	1	70
NG03 status is discharge but status date (Q A.2.) is different from discharge date (Q N.1.)	17	87
NG03 status is death but status date (Q A.2.) is different from death date (Q O.1.)	2	89
Date of death on NG03e differs from date of death on SUPP08	6	95
Date of death on NG03 differs from date of death on SUPP08	2	97
NG05 status is discharge but status date (Q A.2.) is different from discharge date (Q D.1.)	2	99
Infant status on NG03 and SUPP09 are the same but dates are different	24	123
NG03 surfactant date/time is before NG02 birth date/time and/or SUPP03 delivery date/time	12	135
SUPP03 surfactant date/time is before NG02 birth date/time	2	137
SUPP04 surfactant date/time is before NG02 birth date/time	1	138
SUPP03 surfactant date/time does not match NG03 surfactant date/time	19	157
SUPP04 surfactant date/time does not match NG03 surfactant date/time	17	174
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03	14	188
Infant intubated for the 1st time in NICU per SUPP04 but was intubated in DR per SUPP03	1	189
Per SUPP04 indication for NICU intubation was surfactant but surfactant was not given	1	190
DR chest compressions is inconsistent on SUPP03 vs NG03	3	193
Per SUPP03/NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08	37	230
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on SUPP03	1	231
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03	7	238
Per SUPP08 infant had pneumothorax but it is not recorded on NG03	4	242
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03	8	250
Per SUPP09 infant had a HUS at 4-21 days but cranial sonogram is not recorded on NG03	3	253
Per SUPP08 infant had IVH grade 3-4 in 1st 14 days but severe IVH is not recorded on NG03	4	257
Per SUPP08 infant had IVH grade 3-4 on DOL 4-14 but severe IVH is not recorded on SUPP09	2	259
Per NG03 infant had HUS with IVH 3-4 on DOL 4-21 but severe IVH is not recorded on SUPP09	18	277
Per SUPP09 infant had HUS with IVH 3-4 on DOL 4-21 but severe IVH is not recorded on NG03	7	284
Per MRI01 infant had HUS with IVH 3-4 on DOL 1-28 but severe IVH is not recorded on NG03	10	294
Per MRI01 infant had HUS with IVH 3-4 on DOL 4-21 but severe IVH is not recorded on SUPP09	11	305
Per NG03 infant had HUS with PVL on DOL 4-21 but PVL is not recorded on SUPP08	5	310
Per SUPP08 infant had NEC requiring surgery, but per NG03 infant had medical NEC only	1	311
SUPP08 AE entered for DOL >14	12	323

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Secondary cross-form queries (may be >1 per infant)

The FREQ Procedure

Query			
query_num		Frequency	Cumulative Frequency
	SUPP08 AE date is before NG02 birth date	2	325
	Discharge date on NG03 is more than 1 year after birth	1	326
	Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14	15	341

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SUPPORT Cross-Form Queries for Center 21-University of Rochester

Center ID number=21 Network number=70461 NG02 birth date=10/11/05

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 18 but severe IVH is not recorded on SUPP09.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 5 but severe IVH is not recorded on SUPP09.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 8 but PVL is not recorded on SUPP09.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (17:51) does not match SUPP03 delivery time (17:53).				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time ((b) (6)) does not match NG03 surfactant date/time (b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (5:30) does not match SUPP03 delivery time (5:03).				

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG05 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q D.1.)(b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (15:52) does not match SUPP03 delivery time (15:55).				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)				

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.	SUPP08 AE (4=Pulmonary hemorrgage) entered for DOL 42 (b) (6) Please F5 if date is correct or edit date if not.			

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03e(b) (6) differs from date of death on SUPP08 (b) (6)				

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (0:21) does not match SUPP03 delivery time (0:22).				

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (16:45) does not match SUPP03 delivery time (16:04).				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6)) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)	SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)			

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (21:56) does not match SUPP03 delivery time (21:26).	Date of death on NG03e (b) (6) differs from date of death on SUPP08 (b) (6)			

Center ID number=16 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.			

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pneumothorax but it is not recorded on NG03.	SUPP08 AE (1a=Pneumothorax) entered for DOL 33 (b) (6). Please F5 if date is correct or edit date if not.	SUPP08 AE (7=Other) entered for DOL 33 (b) (6). Please F5 if date is correct or edit date if not.		

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03e (b) (6) differs from date of death on SUPP08 (b) (6)				

Center ID number=16 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				

Center ID number=16 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 21 but severe IVH is not recorded on SUPP09.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pneumothorax but it is not recorded on NG03.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (11:22) does not match SUPP03 delivery time (11:30).				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (8:02) does not match SUPP03 delivery time (8:05).				

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (1b=PIE) entered for DOL 16 (b) (6) Please F5 if date is correct or edit date if not.				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (13:54) does not match SUPP03 delivery time (13:34).				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (13:55) does not match SUPP03 delivery time (13:35).	SUPP04 NICU admission date/time (b) (6) is before NG02 birth date/time (b) (6)			

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)) vs (b) (6)			

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=16 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (14:51) does not match SUPP03 delivery time (15:03).	NG03 surfactant date/time (b) (6)) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)			

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SUPPORT Cross-Form Queries for Center 16-University of Alabama

Center ID number=16 Network number=(b) (6) NG02 birth date=12/(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (15:03) does not match SUPP03 delivery time (14:51).	SUPP03 surfactant date/time (b) (6) is before NG02 birth date/time (b) (6).	SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)		

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SUPPORT Cross-Form Queries for Center 15-Stanford University

Center ID number=15 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2. (b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=15 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 20 but severe IVH is not recorded on SUPP09.				

Center ID number=15 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)	SUPP04 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)	Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.		

Center ID number=15 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
DR chest compressions is inconsistent on SUPP03 vs NG03.	Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.			

Center ID number=15 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=15 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6)) is before birth/delivery date/time on NG02 (b) (6)) and/or SUPP03 (b) (6)				

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SUPPORT Cross-Form Queries for Center 15-Stanford University

Center ID number=15 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
DR chest compressions is inconsistent on SUPP03 vs NG03.	Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.			

Center ID number=15 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=15 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=15 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=15 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.				

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SUPPORT Cross-Form Queries for Center 18-University of Texas-Houston

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (.) does not match NG03 surfactant date/time (b) (6)				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)).				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (.) does not match NG03 surfactant date/time (b) (6)				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (18:03) does not match SUPP03 delivery time (18:04).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)) vs (b) (6)			

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 18-University of Texas-Houston

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time(b) (6) is before birth/delivery date/time on NG02 (b) (6)) and/or SUPP03 (b) (6)	SUPP03 surfactant date/time(b) (6)) does not match NG03 surfactant date/time (b) (6)			

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (16:45) does not match SUPP03 delivery time (16:52).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)	Per NG03 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on SUPP09.		

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (22:30) does not match SUPP03 delivery time (22:32).	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had a HUS on DOL 11 but cranial sonogram is not recorded on NG03.				

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.	Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.			

Center ID number=18 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)) vs (b) (6)			

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SUPPORT Cross-Form Queries for Center 18-University of Texas-Houston

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had a HUS on DOL 11 but cranial sonogram is not recorded on NG03.				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.			

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.(b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=18 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)	SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)			

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SUPPORT Cross-Form Queries for Center 14-Brown University

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (7=Other) entered for DOL 15 (b) (6) Please F5 if date is correct or edit date if not.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 18 but severe IVH is not recorded on SUPP09.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03e (b) (6) from date of death on SUPP08 (b) (6)	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (21:42) does not match SUPP03 delivery time (21:33).				

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SUPPORT Cross-Form Queries for Center 14-Brown University

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time=(b) (6) does not match NG03 surfactant date/time=(b) (6)				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (16:00) does not match SUPP03 delivery time (16:03).				

Center ID number=14 Network number=(b) (6) NG02 birth=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time=(b) (6) before birth/delivery date/time on NG02=(b) (6) and/or SUPP03=(b) (6)				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 10 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 10 but severe IVH is not recorded on SUPP09.			

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 14-Brown University

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)			

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 14-Brown University

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.	Per NG03 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.			

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 5 but severe IVH is not recorded on SUPP09.				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

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SUPPORT Cross-Form Queries for Center 14-Brown University

Center ID number=14 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

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SUPPORT Cross-Form Queries for Center 12-Indiana University

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.		

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (6:38) does not match SUPP03 delivery time (6:28).				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (8:45) does not match SUPP03 delivery time (8:58).				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (17:27) does not match SUPP03 delivery time (17:25).				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (20:29) does not match SUPP03 delivery time (18:29).				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) vs (b) (6)			

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SUPPORT Cross-Form Queries for Center 12-Indiana University

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (21:00) does not match SUPP03 delivery time (21:10).				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 21 but severe IVH is not recorded on SUPP09.				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 13 but severe IVH is not recorded on SUPP09.	Per NG03 infant had HUS with IVH 3-4 on DOL 13 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 13 but severe IVH is not recorded on SUPP09.		

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 14 but severe IVH is not recorded on SUPP09.				

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SUPPORT Cross-Form Queries for Center 12-Indiana University

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (1b=PIE) entered for DOL 19(b) (6) Please F5 if date is correct or edit date if not.				

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (11:43) does not match SUPP03 delivery time (11:42).				

Center ID number=12 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was (b) (6) days ago but SUPP09 has not been completed.				

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SUPPORT Cross-Form Queries for Center 12-Indiana University

Center ID number=12 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 13-Yale University

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on SUPP03.	Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.			

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (23:53) does not match SUPP03 delivery time (23:59).				

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=13 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (8:41) does not match SUPP03 delivery time (8:44).				

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SUPPORT Cross-Form Queries for Center 11-University of Cincinnati

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (6:49) does not match SUPP03 delivery time (6:39).				

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pneumothorax but it is not recorded on NG03.				

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was >120 days ago but SUPP09 has not been completed.	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (23:30) does not match SUPP03 delivery time (23:36).				

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 11 but severe IVH is not recorded on NG03.				

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SUPPORT Cross-Form Queries for Center 11 University of Cincinnati

Center ID number=11 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had a HUS on DOL 7 but cranial sonogram is not recorded on NG03.				

Center ID number=11 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 21 but severe IVH is not recorded on NG03.				

Center ID number=11 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03e(b) (6) differs from date of death on SUPP08 (b) (6)				

Center ID number=11 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)	SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)			

Center ID number=11 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (0:53) does not match SUPP03 delivery time (0:45).				

Center ID number=11 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03e(b) (6) differs from date of death on SUPP08(b) (6)				

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SUPPORT Cross-Form Queries for Center 11-University of Cincinnati

Center ID number=11 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution; Center notes
SUPP08 AE (1b=PIE) entered for DOL 18 (b) (6) Please F5 if date is correct or edit date if not.				

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SUPPORT Cross-Form Queries for Center 4-University of Texas-Dallas

Center ID number=4 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=4 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

Center ID number=4 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (5=Death) but dates are differen(b) (6) vs (b) (6)				

Center ID number=4 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on SUPP09.			

Center ID number=4 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (18:46) does not match SUPP03 delivery time (18:45).				

Center ID number=4 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (6:25) does not match SUPP03 delivery time (9:25).				

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SUPPORT Cross-Form Queries for Center 4-University of Texas-Dallas

Center ID number=4 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (14:52) does not match SUPP03 delivery time (12:52).	SUPP04 NICU admission date/time (b) (6)) is before NG02 birth date/time (b) (6)	NG03 surfactant date/time (b) (6)) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)	SUPP04 surfactant date/time (b) (6)) is before NG02 birth date/time (b) (6)	

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SUPPORT Cross-Form Queries for Center 9-Emory University

Center ID number=9 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 13 but severe IVH is not recorded on NG03.				

Center ID number=9 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6)) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=9 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=9 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

Center ID number=9 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=9 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=9 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (20:18) does not match SUPP03 delivery time (20:20).				

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SUPPORT Cross-Form Queries for Center 9-Emory University

Center ID number=9 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (4:31) does not match SUPP03 delivery time (3:46).				

Center ID number=9 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pneumothorax but it is not recorded on NG03.				

Center ID number=9 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 15 but severe IVH is not recorded on SUPP09.	Per NG03 infant had HUS with PVL on DOL 15 but PVL is not recorded on SUPP09.			

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SUPPORT Cross-Form Queries for Center 5-Wayne State University

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6)) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on SUPP09.			

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) not match NG03 surfactant date/time (b) (6)	Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.			

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

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SUPPORT Cross-Form Queries for Center 5-Wayne State University

Center ID number=5 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (0:50) does not match SUPP03 delivery time (0:51).	Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.			

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (0:51) does not match SUPP03 delivery time (0:50).				

Center ID number=5 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=5 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (5=Nasal breakdown) date (b) (6)) is before NG02 birth date (b) (6)				

Center ID number=5 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (5=Nasal breakdown) date (b) (6) is before NG02 birth date (b) (6)				

Center ID number=5 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (22:58) does not match SUPP03 delivery time (22:50).				

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SUPPORT Cross-Form Queries for Center 5-Wayne State University

Center ID number=5 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.				

Center ID number=5 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
DR chest compressions is inconsistent on SUPP03 vs NG03.	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=5 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.	Per SUPP09 infant had HUS with IVH 3-4 on DOL 9 but severe IVH is not recorded on NG03.			

Center ID number=5 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (5=Death) but dates are different (b) (6)				

Center ID number=5 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6)) and/or SUPP03 (b) (6)	SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)			

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SUPPORT Cross-Form Queries for Center 8-University of Miami

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (19:03) does not match SUPP03 delivery time (18:52).				

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP04 indication for NICU intubation was surfactant but surfactant was not given.				

Center ID number=8 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 3-Case Western University

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (7=Other) entered for DOL 23 (b) (6). Please F5 if date is correct or edit date if not.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was >120 days ago but SUPP09 has not been completed.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was (b) (6) days ago but SUPP09 has not been completed.	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had NEC requiring surgery, but per NG03 infant had medical NEC only.				

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SUPPORT Cross-Form Queries for Center 3-Case Western University

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 2 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 3 but severe IVH is not recorded on NG03.			

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (5=Death) but dates are different (b) (6)				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

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SUPPORT Cross-Form Queries for Center 3-Case Western University

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=3 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 26-University of New Mexico

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (14:30) does not match SUPP03 delivery time (14:20).				

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.	Per NG03 infant had HUS with IVH 3-4 on DOL 15 but severe IVH is not recorded on SUPP09.			

Center ID number=26 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

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SUPPORT Cross-Form Queries for Center 26-University of New Mexico

Center ID number=26 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution Center notes
SUPP08 AE (1b=PIE) entered for DOL 16(b) (6) Please F5 if date is correct or edit date if not.	SUPP08 AE (4=Pulmonary hemorrgage) entered for DOL 17 (b) (6) . Please F5 if date is correct or edit date if not.			

Center ID number=26 Network numbe(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution Center notes
SUPP04 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

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SUPPORT Cross-Form Queries for Center 24-University of Iowa

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP08 AE (7=Other) entered for DOL 60 (b) (6) Please F5 if date is correct or edit date if not.				

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 8 but severe IVH is not recorded on NG03.	Per SUPP08 infant had IVH grade 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.			

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (2:53) does not match SUPP03 delivery time (7:53).	Per MRI01 infant had HUS with IVH 3-4 on DOL 6 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 6 but severe IVH is not recorded on SUPP09.		

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant was outborn per NG02 but was enrolled in SUPPORT.				

Center ID number=24 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 25-University of Utah

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (8:34) does not match SUPP03 delivery time (8:39).	Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.			

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (4:43) does not match SUPP03 delivery time (3:46).	SUPP04 NICU admission date/time=(b) (6) is before NG02 birth date/time=(b) (6)			

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (12:10) does not match SUPP03 delivery time (12:11).				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 status following resuscitation was death but per SUPP04 infant was admitted to NICU.				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 25-University of Utah

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (13:27) does not match SUPP03 delivery time (13:40).				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated in DR per NG03 but was not intubated in DR per SUPP03.				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant received chest compressions or epinephrine in the DR but neither was reported on NG03.				

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 8 but severe IVH is not recorded on SUPP09.			

Center ID number=25 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

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SUPPORT Cross-Form Queries for Center 25-University of Utah

Center ID number=25 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 4 but severe IVH is not recorded on NG03.	Per SUPP09 infant had HUS with IVH 3-4 on DOL 4 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 4 but severe IVH is not recorded on NG03.		

Center ID number=25 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 11 but PVL is not recorded on SUPP09.				

Center ID number=25 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

Center ID number=25 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (17:11) does not match SUPP03 delivery time (17:12).				

Center ID number=25 Network number(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 10 but severe IVH is not recorded on SUPP09.				

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SUPPORT Cross-Form Queries for Center 22-University of California-San Diego

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 13 but PVL is not recorded on SUPP09.				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (6:39) does not match SUPP03 delivery time (6:38).				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (9:28) does not match SUPP03 delivery time (9:26).				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (3=Transferred) but dates are different (b) (6)				

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SUPPORT Cross-Form Queries for Center 22-University of California-San Diego

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6)) is different from discharge date (Q N.1.) (b) (6) .	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) (b) (6)	Discharge date on NG03 is more than 1 year after birth.		

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A(b) (6) is different from discharge date (Q N.1.) (b) (6)				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q N.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6) (b) (6)			

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is death but status date (Q A.2.) (b) (6) different from death date (Q O.1.) (b) (6)	Date of death on NG03 (b) (6) differs from date of death on SUPP08 (b) (6)			

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.				

Center ID number=22 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.) (b) (6)) is different from discharge date (Q N.1.) (b) (6)	Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.			

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SUPPORT Cross-Form Queries for Center 22-University of California-San Diego

Center ID number=22 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (17:43) does not match SUPP03 delivery time (17:46).				

Center ID number=22 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant intubated for the 1st time in NICU per SUPP04 but was intubated in DR per SUPP03.				

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (10:42) does not match SUPP03 delivery time (10:24).	NG03e death date/time (b) (6) is before NG02 birth date/time (b) (6)	SUPP03 surfactant date/time (b) (6) is before NG02 birth date/time (b) (6)		

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different (b) (6)				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant was outborn per NG02 but was enrolled in SUPPORT.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is death but status date (Q A.2.) (b) (6) is different from death date (Q O.1.) (b) (6)	Infant status on NG03 and SUPP09 are the same (5=Death) but dates are differen (b) (6)			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (20:00) does not match SUPP03 delivery time (20:05).	Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are differen (b) (6) vs (b) (6)			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG05 status is discharge but status date (Q A.2.) (b) (6) is different from discharge date (Q D.1.) (b) (6).				

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 surfactant date/time=(b) (6) is before birth/delivery date/time on NG02=(b) (6) and/or SUPP03=(b) (6)				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had pulmonary hemorrhage but it is not recorded on NG03.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with PVL on DOL 14 but PVL is not recorded on SUPP09.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 12 but severe IVH is not recorded on SUPP09.			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 11 but severe IVH is not recorded on NG03.	Per MRI01 infant had HUS with IVH 3-4 on DOL 11 but severe IVH is not recorded on NG03.			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG03 status is discharge but status date (Q A.2.)=(b) (6) is different from discharge date (Q N.1.)=(b) (6)				

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SUPPORT Cross-Form Queries for Center 19-Duke University

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP09 infant had HUS with IVH 3-4 on DOL 9 but severe IVH is not recorded on NG03.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was >120 days ago but SUPP09 has not been completed.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per NG03 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.	Per MRI01 infant had HUS with IVH 3-4 on DOL 7 but severe IVH is not recorded on SUPP09.			

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was (b) (6) days ago but SUPP09 has not been completed.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was (b) (6) days ago but SUPP09 has not been completed.				

Center ID number=19 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Birth date was (b) (6) days ago but SUPP09 has not been completed.	Per NG03 infant was hospitalized at 14 days but SUPP05 forms are not entered through DOL 14.			

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SUPPORT Cross-Form Queries for Center 23-Tufts University

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (10:45) does not match SUPP03 delivery time (11:45).				

Center ID number=23 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Date of death on NG03 (b) (6) differs from date of death on SUPP08(b) (6)				

Center ID number=23 Network number(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6) does not match NG03 surfactant date/time (b) (6)				

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP04 surfactant date/time(b) (6) does not match NG03 surfactant date/time(b) (6)				

Center ID number=23 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
SUPP03 surfactant date/time (b) (6)) does not match NG03 surfactant date/time (b) (6)				

Center ID number=23 Network numbe(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (9:40) does not match SUPP03 delivery time (9:42).				

Center ID number=23 Network number=(b) (6) NG02 birth date(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (22:20) does not match SUPP03 delivery time (22:00).				

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SUPPORT Cross-Form Queries for Center 23-Tufts University

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (23:04) does not match SUPP03 delivery time (23:05).				

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP08 infant had IVH grade 3-4 on DOL 37 but severe IVH is not recorded on NG03.	SUPP08 AE (3=Severe IVH) entered for DOL 37 (b) (6) Please F5 if date is correct or edit date if not.			

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (2:32) does not match SUPP03 delivery time (2:31).				

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
NG02 birth time (20:03) does not match SUPP03 delivery time (20:14).	NG03 surfactant date/time (b) (6) is before birth/delivery date/time on NG02 (b) (6) and/or SUPP03 (b) (6)			

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SUPPORT Cross-Form Queries for Center 23-Tufts University

Center ID number=23 Network number=(b) (6) NG02 birth date=(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Per SUPP03 and/or NG03 infant received chest compressions or epinephrine in the DR but AE was not reported on SUPP08.				

Center ID number=23 Network number=(b) (6) NG02 birth date=1(b) (6)

Query 1	Query 2	Query 3	Query 4	Query resolution: Center notes
Infant status on NG03 and SUPP09 are the same (1=Discharged) but dates are different(b) (6)				

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie
Subject: RE: Duke
Date: Thursday, September 03, 2009 10:35:59 AM

Hi,
Yes, DRH is under a separate IRB. We do have all dates of the entire IRB submission process for all the most current studies.

Will keep you posted - no worries - we will have fun when you get back going through this....
Thanks,
Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 03, 2009 8:10 AM
To: Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: Re: Duke

Is Durham Regional covered under the Duke IRB or is it a separate institution - probably separate based on your comments below.
Also, do we have a list of dates for their IRB process for the most recent 3-4 protocols?
Thanks for doing this - sorry I'm not there.

Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Wed Sep 02 22:51:35 2009
Subject: RE: Duke

Primarily missing ROP source ophthal reports (only 2 of the 15 cases had all reports; most didn't have 50%) however, I believe we may be able to rectify this as Kim has asked the eye center to retrieve these. There is one case however that did not report the left eye as having surgery (and they did).

Other problems;

consent issues with the MRI secondary; in the most recent version of the main Support consent, the MRI secondary was rolled into it with an opt in/opt out check box and neither box was check for one or more infants

There is confusion over Durham Regional being a secondary to Duke; apparently they are no longer and have no IRB approvals for nay NRN study

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There have been at lease 6 cases (regarding Marie's recent BPD queries) where Duke has reported status as D/C to home but in reality they were transferred to Durham Regional (which should be status if they are no longer a satellite site). In short; these kids were transferred prior to the 36 wk date and D/C'd home form DRH; they have the wrong status and wrong date of status and are using an F5 comment to let us know they were transferred.

There was one kid withdrawn from study that we did not know about; they competed a PD stating the withdrawal but did not let you or RTI know. This kid's study oximeter was essentially unblinded close to the 36 week date and the PI (Mike C.) found out, decided the kid could no longer be in study). When I talked to Abhik about it he did not this the kid should not have been taken off study; a PD would have sufficed; we do though, have data on this kid - more on that to come.

There was one kid that did not give consent for GDB but did for Support so they held all data (did not transmit support data) until they were to return for FU so they could ask again for GDB consent; this mean we actually have one more kid enrolled to Support we do not currently have counted.

There are minor inconsistencies with data

We have not looked at FU yet; Jamie will be with us tomorrow; more to come then.

This is just a brief, from memory low down; we have everything written down in the monitoring room and Carolyn with have that up in Rockville next Tuesday.

Thanks, and I hope you and all your family are taking care; hope all is relatively well.

Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 02, 2009 10:21 PM
To: Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: Duke

Can you let me know the highlights from today's visit to Duke?
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

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From: Wally Carlo, M.D.
To: Finer, Neil; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: Oxygen Saturation Targeting Paper
Date: Tuesday, September 01, 2009 7:36:55 PM

I think this is the way it happened and the way we should present it. I will add it to the paper.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 01, 2009 6:31 PM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: RE: Oxygen Saturation Targeting Paper

Hi Wally, Rose, Abhik, Marie and Wade
I think one approach would be to write the Methods to be fully descriptive of the study.
In the Introduction, the last paragraph should indicate that we did the study to determine the most appropriate SpO2 level for the treatment of the very preterm infant. The DSMC blinded interim analyses for this trial were made available to the investigators after the trial was complete and the last infant reached 55 weeks of age. They had noted a trend to increased mortality in one of the SpO2 groups which did not reach the predetermined boundary for stopping the trial. The Principal investigators and data center then undertook a safety analyses to evaluate any potential adverse outcomes while waiting for the final ROP diagnosis for all enrolled infants. This analysis did not unblind the investigators to any ROP outcomes by treatment group but evaluated all other available outcomes for which final patient data was available for the randomized infants. We now report the results of these analyses

This will avoid the need to report any ROP outcomes and I suspect that we should report these when we do the follow-up paper.
Let me know what you think
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 01, 2009 2:10 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: Oxygen Saturation Targeting Paper

Dear Marie, Neil, Rose, Abhik, Wade:

I have drafted the tables as requested by Marie. I have also drafted the CONSORT figure so it is easy to identify the gaps. Marie also has the request that we addressed yesterday.

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I am enclosing the 2nd draft of the paper. As agreed, I have changed the focus away from retinopathy. I am still struggling on how to present the primary outcome measure and hypothesis and yet not present the retinopathy methods at the present time or the results in the table. I think we may have to leave the retinopathy in the Methods because that was assessed by the DMC and when we get to the results, we can clarify that we will not be reporting our retinopathy.

I am enclosing the draft 2.0 of the paper with the tables as drafted to make it easier to add additional results.

I am still working to improve the Introduction and Methods. I will write the Results and Discussion next week after I get the data analyzed by Marie.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

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From: Wally Carlo, M.D.
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade
Subject: Oxygen Saturation Targeting Paper
Date: Tuesday, September 01, 2009 5:09:47 PM
Attachments: Oxygen Saturation Targeting.9.1.09.doc

Dear Marie, Neil, Rose, Abhik, Wade:

I have drafted the tables as requested by Marie. I have also drafted the CONSORT figure so it is easy to identify the gaps. Marie also has the request that we addressed yesterday.

I am enclosing the 2nd draft of the paper. As agreed, I have changed the focus away from retinopathy. I am still struggling on how to present the primary outcome measure and hypothesis and yet not present the retinopathy methods at the present time or the results in the table. I think we may have to leave the retinopathy in the Methods because that was assessed by the DMC and when we get to the results, we can clarify that we will not be reporting our retinopathy.

I am enclosing the draft 2.0 of the paper with the tables as drafted to make it easier to add additional results.

I am still working to improve the Introduction and Methods. I will write the Results and Discussion next week after I get the data analyzed by Marie.

Thanks
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Cell: 205 266 (b) (6)

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The Effect of Higher Versus Lower Oxygen Saturation Targeting in Very Premature Infants – The Surfactant Positive Airway Pressure and Pulse Oximetry (SUPPORT) Trial

The SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.

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Word count:

Abstract:

Manuscript:

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

Non randomized studies suggest that the incidence of retinopathy decreases in premature infants with exposure to lower levels of oxygenation than previously maintained but the range of oxygen saturations that reduces retinopathy without increasing adverse outcomes is not known.

Methods

1310 infants of 24 to 27 weeks gestation born at 20 centers of the Neonatal Research Network were randomly assigned at birth to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities among prematurely born infants. The incidence of retinopathy of prematurity is increased with exposure to high levels of oxygenation in premature infants. Oxygen saturation levels previously thought to be in the upper limits of normal appear to increase the risk of retinopathy of prematurity.[1,2,3] Oxygen toxicity may also increase the risk of mortality[4,5], bronchopulmonary dysplasia[6,7] and other morbidities. While data from prospective observational and retrospective studies suggest that maintenance of oxygenation at ranges lower than what have been used may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence regarding the oxygenation levels that reduce retinopathy of prematurity without an increase in adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting, testing the effect of a lower oxygen saturation range (85-89%) as compared to a higher oxygen saturation range (91-95%) on the incidence of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death among infants of 24 to 27 weeks gestational age at birth. The factorial design allowed comparing prophylactic/early surfactant versus continuous positive airway pressure, thus, controlling for the approach to ventilatory support.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and at Research Triangle International (data center) approved the trial. Written informed consent was obtained from the parent or guardian of each participant before delivery.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiples were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks) and by center. Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% with masking using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[8] They were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or to continuous positive airway pressure with a permissive ventilatory strategy. The oxygen saturation values displayed reverted to actual values when less than 85% or greater than 95%. Saturation targeting was initiated within the first two hours after birth. Oxygen saturation targeting with the altered pulse oximetry was continued until 36 weeks post-menstrual age until the infant remained on room air and off the ventilator/ continuous positive airway pressure for more than 72 hours. Infants weaned to room air but who subsequently received oxygen before 36 weeks were placed back on the assigned study pulse oximetry. Adjustments

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in supplemental oxygen to target oxygen saturations were performed by the clinicians, not by the research staff.

Assessments

Data were collected until discharge, were 36 weeks post-menstrual age, or 120 days postnatal age, whichever occurred last. Research nurses recorded all data using standardized definitions. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[9]) was coded if any of the following four findings were present up to 55 weeks post-menstrual age:

If in zone 1:	Stage 3 retinopathy of prematurity, even without plus disease
	Plus disease with any stage retinopathy of prematurity
If in zone II:	Plus disease with stage 2 retinopathy of prematurity
	Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Death was coded up to 36 weeks post-menstrual age for the primary outcome measure. Outcomes included predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of this factorial trial was a logistic regression analysis of the percentages of infants in each group (lower versus higher oxygen saturations) who developed the primary outcome. An absolute difference of 10% between the two treatment groups was considered clinically important. To detect this difference, we planned to enroll 1312 infants for 80% power and a baseline estimated rate of 45% of death/threshold retinopathy/surgery and based on an increase by a factor of 1.12 to account for

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randomizing multiples to the same treatment group and a increase by a factor of 1.17 to account for the expected attrition after discharge and before follow up. The trial was not powered to determine an interaction between the two interventions. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted by the staff at the data center. A two-sided P value of less than 0.05 was considered to statistically significant. Analyses did not include adjustment for multiple comparisons. An independent data safety monitoring committee reviewed the primary outcomes, adverse events and other interim results at ~25%, 50%, and 75% of planned enrollment. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

RESULTS

DISCUSSION

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Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Saturation Group (N = 655)	Higher Saturation Group (N = 661)
Birthweight – g, (M±SD)	835±193	825±193
Gestational age – wk, (M±SD)	26±1	26±1
Male sex – no. (%)	342 (52)	370 (56)
Race or ethnic group – no. (%)		
White	242 (37)	279 (42)
Black	258 (39)	231 (35)
Hispanic	132 (20)	127 (19)
Other	23 (4)	24 (4)
Antenatal corticosteriods – no. (%)	634 (97)	631 (96)
5-min Apgar score < 3 – no. (%)	34 (5)	24 (4)

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Table 2. Major Outcomes

Predischarge outcome – no./total no. (%)	Lower Saturation Group	Higher Saturation Group	Relative Risk (95% CI)
Death before discharge	130/655 (20)	106/660 (16)	
Death by 14 days			
Bronchopulmonary dysplasia by O_2 use at 36 weeks*			
Bronchopulmonary dysplasia (O_2) or death by 36 weeks*			
Bronchopulmonary dysplasia (physiologi)c at 36 weeks*			
Bronchopulmonary dysplasia (physiologic) or death by 36 weeks*			
Intraventricular hemorrhage, grade 3 or 4	93/632 (15)	82/639 (13)	
Intraventricular hemorrhage, grade 3 or 4 or death			
Periventricular leukomalacia	23/631 (4)	32/640 (5)	
Periventricular leukomalacia or death	148/654 (23)	133/660 (20)	
Necrotizing enterocolitis, stage ≥ 2			
Necrotizing enterocolitis, stage ≥ 2 or death			
Late onset sepsis			
Late onset sepsis or death			
Patent ductus arteriosus			
Medical treatment for patent ductus arteriosus			
Surgical treatment for patent ductus arteriosus			
Pneumothorax – no. (%)	30/278 (11)	20/287 (7)	
Other air leaks – no. (%)	30/278 (11)	20/287 (7)	

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Postnatal steroids for bronchopulmonary dysplasia	62/637 (10)	68/642 (11)

* In babies alive at 36 weeks post-menstrual age.

Table 3. Other Outcomes

	Lower Saturation Group	Higher Saturation Group	P value
Length of stay, M+SD, days*	98±37	102±43	0.16
Oxygen after discharge – no./total no. (%)	115/518 (22)	126 (543) 23	0.07
Duration of mechanical ventilation, M+SD*, days*	19±23	22±24	0.13
Duration of oxygen supplementation, M+SD, days	51±38	60±36	< 0.001
Continuous positive airway pressure, M+SD, days*	16±14	16±14	0.98
Nasal synchronized intermittent mandatory ventilation, M+SD, days*	3±6	4±7	0.07
Alive off mechanical ventilation by day 14, M+SD, days			

*For survivors to discharge or up to 120 days only

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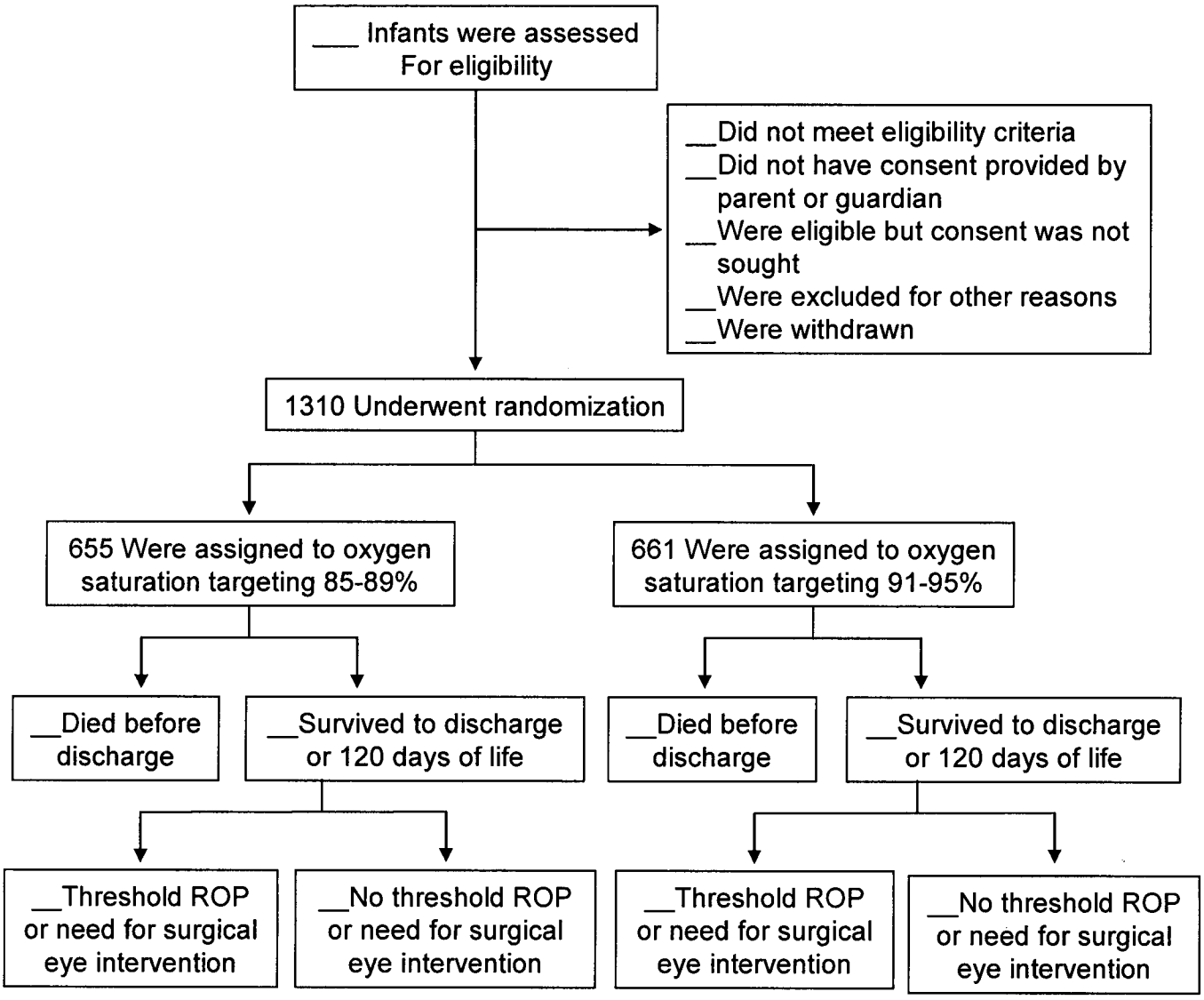
Figure 1



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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B; Dusick, Anna M.; "Gantz, Marie"
Subject: RE: ****SUPPORT******
Date: Tuesday, September 01, 2009 3:46:36 PM

From: Hamer, Faithe Angeline
Sent: Tuesday, September 01, 2009 3:38 PM
To: Wilson, Leslie Dawn
Subject: RE: ****SUPPORT******

(b) (6) - appt tomorrow
(b) (6)- visit complete - forms to be entered
(b) (6)- visit complete - forms to be entered

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
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699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312(b) (6) (pager)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 10:11 AM
To: Poindexter, Brenda B; Wilson, Leslie Dawn; Dusick, Anna M.
Cc: mgantz@rti.org
Subject: ****SUPPORT******

Hi - We need the following SUPPORT outcomes. Thanks for all your help.

Rose

12 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.
12 (b) (6) FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.
12 (b) (6) FU marked as complete (per NF10/SF10) but NF05 has not been completed.

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From: Finer, Neil
To: "wcarlo@peds.uab.edu"; "adas@rti.org"; "mgantz@rti.org"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Date: Tuesday, September 01, 2009 2:16:39 PM
Attachments: SUPPORT CPAP vs Surf Sept 1 09.docx
Tables Aug 29.docx

Hi Guys
Thanks for yesterday – a tumultuous day to say the least. Marie – you are great and thanks for being so patient and doing the analyses – over and over and over!!!
Well, Wally will no doubt be surprised at the outcome but here it is
I decided that the gender difference is too large to ignore p=.054 and asked that we adjust for it
We did and no more significance for Death/BPD
That's the truth and so be it!!
It looks like both papers will be about death, decreased by 8% for our small strata or NNT of 12.5 for infants of 24-25 wks as good as I have ever seen. All directions of BPD are better as is time on vent, need for PNS etc and there are no increased adverse outcomes
So I have rewritten the manuscript for all of your reviews
Marie please check the actual p values and correct them - I estimated from what I remembered
Please also correct the tables where needed if at all.
The paper is about 400 words too long so everyone can slash and burn
Wally we will go together to the NEJM. The 2 papers provide a balance and the negative message for SpO2 is offset by the positive in CPAP –
Who knows what the journal will accept – but we are completely in keeping with our protocol, manual and web info
Let's try to get these to the journal within 4 weeks - that would deal with the need to provide the other trials with needed data – we can also do that sooner if we want -I propose a Subcommittee meeting in 2 weeks when they can all see both manuscripts
I would keep still about everything till then – Marie and Abhik can check the data and stats so we have it right.
I don't feel a need to rush with our data anymore – I think having it peer reviewed would be good and our DSMC should also have a chance to see the outcomes and provide feedback and counsel about discussing our outcomes with the other trials
Big breath in !!!!!
Neil

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation.

Methods: The SUPPORT study was a randomized multicenter factorial trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical estimate within 2 prospective strata, 24 to 25 6/7ths weeks, and 26 to 27 6/7th weeks. Infants randomized to CPAP were treated with CPAP initiated in the delivery room and were subsequently treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1316 infants from February 2005 to February 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.001$). There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.015$). All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, ($p<0.001$). There were no differences between the groups for airleaks including penumothoraces. The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, (unadjusted $p = 0.035$, $p= 0.042$ when adjusted for gestational age, center and familial clustering and gender). There was a significantly lower mortality in the 24 to 25 weeks strata for the infants in the Surfactant arm, (24% vs 32%, unadjusted $p=0.026$, adjusted $p=.04$).

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or survival with BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22

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months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no agreement as to the optimal approach for the extremely low birth weight (ELBW) infant following delivery. Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC) and continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[4] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[5]

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from both the US and other countries.[67] These reports have documented a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[8910]

The current available evidence demonstrates that prophylactic and early surfactant treatment at less than 2 hours of life significantly decreases mortality, air leak, and BPD in preterm infants.[1112] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants and has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI). [13]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age, and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation

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or CPAP received 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group, most occurring within the first 2 days (9.1% vs 3.0%, p=.001), consistent with the findings of an earlier meta analyses4 and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) with no difference in death or BPD at 36 weeks.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this study was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at a randomizing center, for which a decision has been made to provide full resuscitation without known malformations, and for whom parental consent had been obtained. The infants were randomized to 2 gestational age strata, 24 0/7ths to 25 6/7ths weeks, and 26 0/7ths-27 6/7ths weeks.

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CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP both at a recommended 5 cm H_2O was utilized if the infant required positive pressure during resuscitation. CPAP was continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery . While intubation was never required by protocol, CPAP infants could be intubated if they met any of the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50% , a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for Intubation for the CPAP infants. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 $\leq$ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any

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time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, (using the NRN occurrence of death or survival with BPD of 67% using the year 2000 data), and the occurrence of death or survival with neurodevelopmental impairment (NDI) at 18 to 22 months (using the NRN occurrence of NDI of 61% using year 2000 data) by 10%. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [15,16]

Statistical analyses: Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses was a logistic regression analysis of the percent of each Group who developed their respective outcome measure of survival without BPD at 36 weeks and on the percent infants who survive without neurodevelopmental sequelae at 2 years. Adjustment was performed as pre-specified for gestational age, center and familial clustering. A two-sided P value of less than 0.05 was considered to statistically significant. An independent data safety monitoring committee reviewed the interim results, including those concerning adverse outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

The study was approved by Human Subjects Committees at all participating sites and RTI, the data center, and parental consent was required before delivery.

Results:

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There were 1361 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009. The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 with no protocol changes. The patient descriptive information for the CPAP versus Early Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight Apgar scores or race between the 2 groups, although there were more boys in the CPAP arm, p=.056. The Surfactant group received significantly more epinephrine in the delivery room and had a higher DR mortality which was not significant.

In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$, Table 2.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p = 0.0354$, $p= 0.0424$ when adjusted for gestational age, center and familial clustering). There was a non-significant reduction in the occurrence of BPD using the need for supplemental oxygen, 40% vs 44%, p=.121 unadjusted, and p=.214 adjusted. Using the Physiologic Definition for BPD there was a non-significant decrease in the occurrence of BPD in the CPAP group (39% vs 41%, p=.63), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=.248). In view of the greater proportion of males in the Surfactant arm, we elected to do a further adjustment for gender, which reduced the significance of the primary outcome for death and BPD using oxygen alone to p=.07 and further increased in the p value for the primary using the Physiologic definition of BPD.

There were no differences overall for death in the delivery room nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 3). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.0149$). We prospectively recorded air leaks in the first 14 days and there were no differences between the groups, and no differences for medical or surgical NEC, PDA requiring surgery, severe IVH or airleaks during the hospital stay. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs13%, $p=0.0004$). Death during the hospitalization was 4% lower for

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the CPAP group overall, and was significantly lower in the CPAP arm the 24 to 25 week strata even after adjustment which included gender.

Strata Results: 24 – 25 weeks Gestation

There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group **(Marie – I think we adjusted for this please indicate this - please correct all my estimated p values for the adjusted outcomes – Thanks)** The differences are shown in Table 4 (24-25 wk Strata). CPAP infants had a significantly lower mortality (24% vs 32%, p=0.0264, p=.04 after adjustment for gestational age, center, familial clustering and gender. There was a significantly higher exposure to postnatal steroids for BPD, 21% vs 13%, p=0.0198) for the Surfactant group, and there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants in this strata.

26-27 weeks Gestation

There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p=0.0097, lesser days of mechanical ventilation, 10.7 vs 14.2, p=0.0068, and less postnatal steroids for BPD, 3% vs 8%, p=0.0027.

Discussion:

The SUPPORT trial is the first large multicenter study to prospectively compare early CPAP, with early surfactant given within an hour of life to a large group of ELBW infants. The current trial is the largest study reported to prospectively compare the use of early CPAP and early surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[17] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[18]

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Our study differs from the recently reported COIN trial14 in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation, and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our methodology of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation. **Error! Bookmark not defined.** We believed that testing this complete approach would be provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation.

Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. As with any prospective randomized trial differences may exist in baseline characteristics and we noted more males in our Surfactant arm. While this difference did not reach significance, we believed that the clinical significance of this difference was relevant and chose to further adjust our results for gender which resulted in a loss of significance for our primary outcome variable using the definition of BPD as requiring oxygen at 36 weeks age. However we also noted a very significant 8% reduction in death in our 24 to 25 week strata resulting in a number needed to treat of 12.5 for each additional survivor. The 565 infants in our 24 to 25 week strata to our knowledge represents the largest prospective group of such immature infants to be randomized in any neonatal trial evaluating respiratory interventions. We believe that this lower incidence of death in these infants along with a reduction of BPD and decreased durations of ventilation and exposure to post natal steroids in the overall CPAP group represents a substantial clinical benefit compared with the initial use of early surfactant.

Our rates of BPD are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defined as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. We did not find an increase in airleaks with the use of early CPAP at 5 cm H2O.

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The SUPPORT study was designed as a factorial design with each infant randomly receiving 2 interventions, CPAP vs Surfactant, and a lower versus higher SpO2 target range. While the study was not powered to detect an interaction between the 2 interventions, we did prospectively agree to evaluate such interactions and none were found. Both arms of the study were adequately powered for both the outcomes at neonatal discharge and the occurrence of survival NDI at 18 to 22 months and these results will be presented after all survivors have been assessed.

Conclusions:

ELBW infants between 24 and 27 6/7ths weeks gestation at birth treated with CPAP and a permissive ventilator strategy compared with the use of surfactant within 1 hour of birth and conventional mechanical ventilation have a decreased incidence of death or survival with BPD based on the need for oxygen at 36 weeks PCA with no demonstrable increase in any adverse neonatal outcomes. Early CPAP and a permissive ventilator strategy is associated with a significant reduction in mortality in the most immature infants. Surviving infants will have a complete neurodevelopmental evaluation at 18 to 22 months and these results will be separately reported.

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Table 1. Demographic Information for randomized infants

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0552

Table 2. Delivery Room interventions

Variable	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Apgar at 1 minute <3	23% (154/662)	26% (167/652)	0.3214
Apgar at 5 minutes <3	4% (26/664)	5% (32/652)	0.3806
PPV in the DR (per SUPP03)	66% (435/662)	93% (605/651)	<0.0001*
CPAP in the DR (per SUPP03)	81% (539/663)	22% (146/652)	<0.0001*
Surfactant in DR (per SUPP03)	14% (93/659)	51% (334/651)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)	67% (443/660)	99% (645/652)	<0.0001*
Chest compressions in DR (per SUPP03)	5% (36/660)	6% (40/652)	0.5978
Epinephrine in DR (per SUPP03)	2% (13/660)	4% (27/652)	0.0222*
Death in the DR (per SUPP03/SUPP04)	0% (1/663)	1% (6/652)	0.0552

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Table 3. Other Outcomes

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
Death in the first week	6% (40/664)	6% (39/651)	0.9797
Death at any time while hospitalized	16% (109/664)	20% (127/651)	0.1440
Total LOS any hospital (survivors only)	99.9 ± 42.6	100.5 ± 39.4	0.8210
Days on supplemental oxygen (survivors only)	53.9 ± 37.2	57.4 ± 37.0	0.1138
Days on mechanical vent (HFV & CV) (survivors only)	19.0 ± 22.8	22.0 ± 24.8	0.0392*
Days on CPAP (survivors only)	16.1 ± 13.2	16.0 ± 14.6	0.9229
Discharge on oxygen	22% (120/547)	24% (121/514)	0.5334
Alive and off MV (HFV/CV) at 7 days	55% (362/654)	49% (316/650)	0.0149*
Any air leak in first 14 days	7% (44/664)	8% (49/652)	0.5293
Medical or surgical NEC	13% (83/655)	10% (62/634)	0.1004
PDA requiring surgery	11% (73/654)	11% (68/634)	0.8019
IVH grade 3-4	15% (95/644)	13% (80/627)	0.3027
Postnatal steroids for BPD	7% (47/650)	13% (83/629)	0.0004*

Table 4. 24 to 25 week Strata

Characteristic	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Death in the first week	9% (25/285)	10% (29/279)	0.5127
Death at any time while hospitalized	24% (68/285)	32% (90/279)	0.0264*
Total LOS any hospital (survivors only)	120.0 ± 47.4	118.6 ± 39.6	0.7514
Days on supplemental oxygen (survivors only)	75.7 ± 34.1	76.8 ± 33.1	0.7500
Days on mechanical vent (HFV & CV) (survivors only)	32.1 ± 26.6	35.8 ± 27.8	0.1672
Days on CPAP (survivors only)	18.6 ± 13.9	17.7 ± 15.5	0.5496
Discharge on oxygen	32% (68/212)	31% (57/185)	0.7867
Alive and off MV (HFV/CV) at 7 days	34% (97/282)	26% (73/279)	0.0339*
Any air leak in first 14 days	8% (22/285)	10% (28/280)	0.3399
Medical or surgical NEC	15% (42/279)	13% (34/267)	0.4338
PDA requiring surgery	16% (46/279)	18% (47/267)	0.7289
IVH grade 3-4	19% (53/273)	19% (50/265)	0.8722
Postnatal steroids for BPD	13% (36/276)	21% (54/263)	0.0198*

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From: Vohr, Betty
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ***SUPPORT*****
Date: Tuesday, September 01, 2009 10:17:44 AM

See below.

-----Original Message-----
From: Ventura, Suzy
Sent: Monday, August 31, 2009 9:09 AM
To: Vohr, Betty
Subject: RE: ***SUPPORT*****

(b) (6) is coming in October and Nina already has her on the list for network and ROP.
(b) (6) is Angelita's

-----Original Message-----
From: Vohr, Betty
Sent: Friday, August 28, 2009 7:44 PM
To: Ventura, Suzy
Subject: FW: ***SUPPORT*****

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 10:15 AM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita
Cc: mgantz@rti.org
Subject: ***SUPPORT*****

Hi,
We are missing a few support outcomes - thanks for all your help

Rose
14 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
CENTER NETWORK BPD_message
14 (b) (6) NG07 section C is filled out but the PHY01 is also expected because this is a SUPPORT infant.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; "kzaterka@rti.org"
Cc: "adas@rti.org"; "mgantz@rti.org"; Rich, Wade; "wcarlo@peds.uab.edu"
Subject: RE: Re:
Date: Monday, August 31, 2009 3:49:49 PM

Hi Rose
The LowSpO2 group overall actually were bigger at birth, and had less males, and we adjusted for GA, Familial clustering – we will look at the occurrence of multiples between the arms.
We then did the gender - We will work on getting the best data set and not attempt to force the ROP data at present. We agree with informing the DSMC.
We believe the most prudent approach is to rapidly report this trial to provide the best data for all other investigators. We believe that we , the investigators should be the group that informs others – Not the DSMC as this study is complete.
Neil and Wally

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 31, 2009 12:42 PM
To: Finer, Neil; 'kzaterka@rti.org'
Cc: 'adas@rti.org'; 'mgantz@rti.org'; Rich, Wade; 'wcarlo@peds.uab.edu'
Subject: Re:

This is a safety issue and should go to the DSMC. For the low sat arm- are we sure that there were not confounding factors that would have raised the mortality rate such as lower GA, lower BW, more multiples or higher order multiples (as these infants may have higher mortality) that could account for the deaths?

Thanks for your thoughts.

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Das, Abhik' <adas@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; Rich, Wade <wrich@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Mon Aug 31 15:17:43 2009
Subject:

Hi Rose
We have been reviewing the SUPPORT outcomes and we thought that you would want to know – a little distraction for you. We noted an increase in death in the Low SpO2 vs Hi SpO2 strata that was p=.07. We then ran the usual adjustments for GA, center and familial clustering and the p value was p=.0499. We the noted that there were more boys in the Hi SpO2 strata and then adjusted for gender and the p=.0378.
The ROP data is not good – too many missing values – we will try to get better info but this is not going to be clean. I think that we need to fast track a manuscript to NEJM regarding the increase

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mortality in the Low SpO2 strata. We will look at causes of death. All of us think that we should do this and also discuss with the DSMC as soon as we can.

We thought you would want to know – we are still hashing this out.

(b) (6) [redacted]

Neil, Wally, Wade; Abhik, Marie

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "gloria.siaw@duke.edu"
Cc: "cotte010@mc.duke.edu"; "goldb008@mc.duke.edu"; "golds005@mc.duke.edu"; "kimberly.fisher@duke.edu"; "mgantz@rti.org"
Subject: Re: ****SUPPORT OUTCOMES*****
Date: Saturday, August 29, 2009 3:55:02 PM

Thanks
Rse
Rosemary D. Higgins, MD
Program Scientist

From: Gloria Siaw <gloria.siaw@duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'cotte010@mc.duke.edu' <cotte010@mc.duke.edu>; 'goldb008@mc.duke.edu' <goldb008@mc.duke.edu>; 'golds005@mc.duke.edu' <golds005@mc.duke.edu>; 'kimberly.fisher@duke.edu' <kimberly.fisher@duke.edu>; 'mgantz@rti.org' <mgantz@rti.org>
Sent: Sat Aug 29 14:49:20 2009
Subject: Re: ****SUPPORT OUTCOMES*****

Hi Rose,

All SUPPORT BPD queries have been resolved and entered into the database as of August 25, 2009. There are no outstanding queries as of this moment.

Thanks,

GS

Gloria Siaw, BSN, BS, CRA
Clinical Research Coordinator
Dept of Pediatrics/Neonatology
2424 Erwin Road - Suite 504
DUMC Box 2739
Durham, NC 27705
Phone: 919 - 681- 5859
Pager: 919-970(b) (6)
Fax: 919 - 681- 4868
Email: - gloria.siaw@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/29/2009 08:32 AM

To "'gloria.siaw@duke.edu'" <gloria.siaw@duke.edu>
cc "'cotte010@mc.duke.edu'" <cotte010@mc.duke.edu>, "'goldb008@mc.duke.edu'" <goldb008@mc.duke.edu>, "'golds005@mc.duke.edu'" <golds005@mc.duke.edu>, "'kimberly.fisher@duke.edu'" <kimberly.fisher@duke.edu>, "'mgantz@rti.org'" <mgantz@rti.org>
Subject Re: ****SUPPORT OUTCOMES*****

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Thanks for all the effort!
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Gloria Siaw <gloria.siaw@duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; kimberly.fisher@duke.edu <kimberly.fisher@duke.edu>; mgantz@rti.org <mgantz@rti.org>
Sent: Fri Aug 28 19:59:15 2009
Subject: Re: ****SUPPORT OUTCOMES*****

Hi Rose,

Please see below the final results of the ROP's highlighted in purple.

Thanks,

GS

19 (b) (6) The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders. **Completed and has entered into the database**

19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Eye exams have been completed, waiting for report from Ophthalmologist.

19 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. **Pt has Follow-up visit schedule in Sept.**

19 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. **Pt has Follow-up visit schedule in Sept.**

19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. **Has been completed and entered into the (DBMS)**

19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. **Pt was originally scheduled to see an ophthalmologist on Dec 1st. We called the Ophthalmologist to change the appt to earliest date available. Awaiting to hear from the ophthalmologist.**

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye. Eye exams have been completed, (b) (6) waiting for report from Ophthalmologist.

19 (b) (6) No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early. Eye exams have been completed, (b) (6) waiting for report from Ophthalmologist.

Gloria Siaw, BSN, BS, CRA
Clinical Research Coordinator
Dept of Pediatrics/Neonatology
2424 Erwin Road - Suite 504
DUMC Box 2739
Durham, NC 27705
Phone: 919 - 681- 5859
Pager: 919-970-(b) (6)
Fax: 919 - 681- 4868

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Email: - gloria.siaw@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/28/2009 10:27 AM

To "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, " (gloria.siaw@duke.edu)" <gloria.siaw@duke.edu>, "kimberly.fisher@duke.edu" <kimberly.fisher@duke.edu>, "golds005@mc.duke.edu" <golds005@mc.duke.edu>

cc "mgantz@rti.org" <mgantz@rti.org>

Subject ****SUPPORT OUTCOMES*****

We are missing the following SUPPORT outcomes. PLease enter them as soon as possible.

Thanks
Rose

19 (b) (6) The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
19 (b) (6) No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

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From: Gantz, Marie
To: Hale, Ellen; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Subject: RE: ******SUPPORT*****
Date: Friday, August 28, 2009 7:31:28 PM

Hi Ellen,
You are correct, those two cases were not from your center, so please disregard them.
Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Hale, Ellen [mailto:ehale@emory.edu]
Sent: Friday, August 28, 2009 11:12 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Cc: Gantz, Marie
Subject: RE: ******SUPPORT*****

Rose,
See comments below. I do not think (b) (6) and (b) (6) belong to us. These 2 children were not in SUPPORT at our center.

Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 10:09 AM
To: Hale, Ellen; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Cc: mgantz@rti.org
Subject: ******SUPPORT*****

Hi
We urgently need the followinng missing SUPPORT outcomes. let us know how you are doing.

thanks for all your help

Rose
CENTER NETWORK ROP_message

9 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
Lost
9 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
Still working on this one.
9 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for

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Lost
CENTER NETWORK FU_message
(b) (6) FU window has closed but NF05 and NF09a have not been completed.
Not our subject
(b) (6)
Not our subject

9 (b) (6) FU window has closed but NF05 and NF09a have not been completed.
Cannot locate--will need to code as lost
9 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed.
Forms have been entered--visit complete
9 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed.
Forms have been entered--visit complete.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ******SUPPORT*****
Date: Friday, August 28, 2009 7:30:46 PM

Hi Rose,
Those cases were from center 5 and were listed as such on the spreadsheet I sent you. I will let Ellen know not to worry about them.
By the way, I'm sorry to hear that your dad is not doing well. My thoughts are with you and your family.
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 11:15 AM
To: Gantz, Marie
Subject: Fw: ******SUPPORT*****

Can you check on the two that don't belong to Emory?
Rosemary D. Higgins, MD
Program Scientist

From: Hale, Ellen <ehale@emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>; Ellen Hale <Ellen.Hale@oz.ped.emory.edu>; Ira Adams-Chapman <Ira_Adams-Chapman@oz.ped.emory.edu>
Cc: mgantz@rti.org <mgantz@rti.org>
Sent: Fri Aug 28 11:11:35 2009
Subject: RE: ******SUPPORT*****

Rose,
See comments below. I do not think (b) (6) and (b) (6) belong to us. These 2 children were not in SUPPORT at our center.

Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 10:09 AM
To: Hale, Ellen; Barbara Stoll; Ellen Hale; Ira Adams-Chapman
Cc: mgantz@rti.org
Subject: ******SUPPORT*****

Hi
We urgently need the followinng missing SUPPORT outcomes. let us know how you are doing.

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thanks for all your help

Rose
CENTER NETWORK ROP_message

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Lost
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From: Wally Carlo, M.D.
To: Finer, Neil; Gantz, Marie; Zaterka-Baxter, Kristin; Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP documents
Date: Friday, August 28, 2009 5:13:09 PM

Great!

See you on Monday.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, August 28, 2009 2:57 PM
To: Wally Carlo, M.D.; Gantz, Marie; Zaterka-Baxter, Kristin; Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP documents

Hi Guys
Here is my first cut at the paper
We need to agree on many things but a place to start discussing
See you soon
Thanks for your draft Wally
Safe travels
Neil

mailto:WCarlo@peds.uab.edu]
Sent: Friday, August 28, 2009 9:03 AM
To: Gantz, Marie; Finer, Neil; Zaterka-Baxter, Kristin; Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
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Dear Neil, Rosemary, Rich, Abhik, Kristin, and Marie:

Enclosed is a first draft of the oxygen saturation paper. The Introduction and Methods are complete. I have not worked on the rest of the pending results and/or interpretation of them.

See you on Wednesday.
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Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology

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Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 2:56 PM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Neil,

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Thanks, everyone, for your help in this. I know it's a lot to look at, but it will help us ensure that our primary outcome data are as clean as possible.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, August 27, 2009 3:42 PM
To: Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
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Hi Marie
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Threshold (New Type I) ROP is defined as:
• In Zone II: plus disease with stage 2 or stage 3
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Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 11:37 AM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: ROP documents

Hi all,

Please find attached four ROP documents for your review (described below). Before we do the ROP analysis, we will need to clean the ROP data as we have been doing for BPD. This will likely involve sending out a batch of queries for the centers to resolve inconsistencies within and between forms. As I am less familiar with ROP than I am with the BPD outcomes, I will need your help to identify inconsistencies that need to be resolved. The attached documents were created in order to facilitate that process. Perhaps we can review them together during our meeting on Monday.

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I look forward to reviewing the SUPPORT data with you next week.

Thanks,
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From: Finer, Neil
To: "Wally Carlo, M.D."; Gantz, Marie; Zaterka-Baxter, Kristin; Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP documents
Date: Friday, August 28, 2009 3:57:17 PM
Attachments: SUPPORT CPAP vs Surf August 27 09.docx

Hi Guys
Here is my first cut at the paper
We need to agree on many things but a place to start discussing
See you soon
Thanks for your draft Wally
Safe travels
Neil

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Phone: 205 934 4680
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To: Finer, Neil; wacarlo@uab.edu
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Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Address correspondence to

Neil Finer, MD

402 Dickenson St, 8774

San Diego, Ca, 92103-8774

Email – nfiner@ucsd.edu

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Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation. No study to date has compared these approaches in a large population of ELBW infants

Methods: The SUPPORT study was a randomized multicenter trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical within 2 prospective strata, 24 to 25 6/7ths weeks, and 26 to 27 6/7th weeks. Infants randomized to CPAP were treated with CPAP initiated in the delivery room and continued following admission to the NICU and such infants could be intubated if they met prespecified criteria including an FiO2 >.50 required to maintain an indicated SpO2 > 88% for one hour, an arterial PaCO2 > 65 torr , and/or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. Criteria for extubation differed between the 2 groups with the CPAP infants treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1316 infants from February 2005 to February 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, APGAR scores or race between the 2 groups. There were no differences between the groups in the receipt of any or a full course of antenatal steroids, or compressions in the DR, whereas the Surfactant group received significantly more epinephrine in the delivery room (4% vs 2%, p=0.022). In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all p<0.001). There were no differences overall for death in the delivery room or death during the hospitalization, nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015). There were no differences between the groups for airleaks including penumothoraces, and no

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differences for medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, ($p<0.001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants , 7% vs 13%, $p=0.0004$). The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, ($p = 0.035$, $p= 0.042$ when adjusted for gestational age, center and familial clustering). There was a significantly higher mortality (32% vs 24%, $p=0.026$) in the 24 to 25 weeks strata for the infants in the Surfactant arm.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or survival with BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

Introduction:

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

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Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[1]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours (+12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[2] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[3]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation.[4] CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[5] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era found that early CPAP improved survival overall and for infants greater than 1500 gm, and was associated with increased pneumothoraces.[6] A more recent review of prophylactic CPAP started in the delivery room reviewed only 2 available trials and found no significant difference between the CPAP and conventionally managed infants and noted a trend to increased adverse outcomes for the CPAP treated infants.[7] These authors concluded that there was insufficient evidence to evaluate the use of prophylactic nasal CPAP in preterm infants.

There is substantial retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, which preferentially utilized early CPAP had the lowest rate of CLD when compared to other units. [8] More recent comparisons of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993 and with units in Stockholm which also used early CPAP . demonstrated that the units using early CPAP had less CLD or less oxygen dependency at 40 weeks postconceptional age. [910] Similar observations were reported by a number of other European centers who noted a decrease in the need for mechanical ventilation among their very preterm infants without an increase in morbidity following the initiation of early CPAP treatment.[111213]

The recent COIN trial randomized 610 infants from 25 weeks 0 days to 28 weeks 6 days gestational age at birth, who were able to breathe at 5 minutes of age, and had evidence of respiratory distress at that time. Infants were randomized to either intubation and ventilation or CPAP received 8 cm H20. CPAP infants were intubated if they met failure criteria.[14] This study did not compare early CPAP to the early administration of surfactant, and surfactant use followed unit standard of care. The results demonstrated that there was no difference between the groups for the outcome of death or BPD by the need for oxygen at 36 weeks. There was a significant primary increase in the occurrence of pneumothoraces in the CPAP group, most

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occurring within the first 2 days (9.1% vs 3.0%, p=.001), consistent with the findings of an earlier meta analyses6 and a reduction in death or the need for oxygen at 28 days in the CPAP infants (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006) .

At the present time there are no studies in the surfactant and antenatal steroid era which have prospectively compared early CPAP with the use of prophylactic or early surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.[15] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[16] Overall surfactant has not been reported to significantly reduce BPD, but may do so for the most immature infants.[17] In addition surfactant has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI), but has reduced death and not been associated with increased NDI in such survivors.

In view of the current interest in the use of early CPAP and the lack of prospective comparisons of this approach with the evidence based intervention of prophylactic or early surfactant, the SUPPORT study was designed to compare these approaches for the most preterm infants. We also randomized infants to 2 ranges of pulse oximetry targets during their exposure to oxygen using a factorial design, and the results for the oximetry study will be reported separately.

Methods

This was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This report describes the prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (< 1 hour) surfactant and mechanical ventilation.

Infants were also randomized to a prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant was no longer requiring ventilatory support using purpose altered oximeters. These results will be separately reported.

The primary hypothesis of this study was that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

Eligible infants were 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born at the randomizing center, for which a decision has been made to provide full resuscitation as

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required without known malformations, and for whom parental consent had been obtained, with 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks.

CPAP Arm - Delivery room management: A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used at all sites for the delivery room administration of CPAP. CPAP or ventilation with PEEP was utilized if the infant requires positive pressure during resuscitation. CPAP was continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. CPAP infants were not to be intubated for surfactant only in the DR, and CPAP infants who required intubation for resuscitation were to receive surfactant within 60 minutes of birth. Intubation for these infants was performed only for the standard NRP indications including failure to respond to positive pressure ventilation (PPV) with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

NICU management: Intubation was performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery . While intubation was never required by protocol, CPAP infants could be be intubated if they meet ***ANY*** *of* the following criteria: an FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% for one hour, an arterial $PaCO_2$ > 65 torr documented on a single blood gas, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life infants were to receive surfactant.

Extubation for CPAP infants was to be attempted within 24 hours if ALL of the following criteria were met: a PaCO2 < 65 torr with a pH > 7.20, an SpO2 > 88% with an FiO2 < 50% , a mean airway pressure (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for Intubation for the CPAP infants. After 3 intubations CPAP infants were treated using NICU standard of care.

Surfactant Arm: All such infants were to be intubated within 1 hour of life and receive surfactant, followed by continued ventilation. All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30 An FiO2 ≤ 35 with a SpO2 > 88%, a mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and be hemodynamically stable with no evidence of clinically significant PDA. Once extubated Surfactant infants were treated using NICU standard of care.

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These criteria were in effect for the first 14 days of life, following which the infant was treated as per NICU standard of care. For both arms of the trial intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Randomization was stratified by gestational age group, utilizing specially prepared double-sealed envelopes. Deliveries were randomized as a unit, and thus multiples, were randomized to the same arm of the trial.

Hypothesis and sample size: We hypothesized that early CPAP would reduce the incidence of death or survival with BPD at 36 weeks, and the occurrence of death or survival with neurodevelopmental handicap at 18 to 22 months by 10% using the NRN occurrence of these outcomes for infants born in 2000. We increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduced a clustering effect into the design, and increased the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This resulted in a sample size of 1312 infants. This sample size was not large enough to determine an interaction effects between the 2 factorial arms.

In addition there was a prospective decision to also evaluate the occurrence of BPD using the Physiologic Definition which required an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks and assigned a diagnosis of BPD to any infant who required more than 30% oxygen at 36 weeks or who required positive pressure support. [1819]

The study was approved by Human Subjects Committees at all participating sites and RTI, the data center, and parental consent was required before delivery.

Results:

There were 1361 infants enrolled in this trial from Jan 1 2004 through to Mar 1 2009. The trial was temporarily suspended by the DSMB because of concerns regarding the oximetry data in November 2005 but after a complete review the trial was continued in February 2006 (Check dates) with no protocol changes. The patient descriptive information for the CPAP versus Early Surfactant arms is shown in Table 1.There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight Apgar scores or race between the 2 groups, although there were more boys in the CPAP arm. In addition there were no differences in the maternal receipt of any or a full course of antenatal steroids, or compressions in the DR, whereas the Surfactant group received significantly more epinephrine in the delivery room and had a higher DR mortality which was not significant.

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In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all $p<0.0001$). Intubation in the DR occurred in 34% of CPAP infants compared with 93% of surfactant infants, $p<0.0001$.

The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was significantly lower for the CPAP group compared with the Surfactant group, 48% versus 54%, ($p = 0.0354$, $p= 0.0424$ when adjusted for gestational age, center and familial clustering). Using the Physiologic Definition for BPD there was a non-significant decrease in the occurrence of BPD in the CPAP group (39% vs 41%, p=.63), and a non-significant reduction in the occurrence of death or Physiologic BPD at 36 weeks in the CPAP group, (48% vs 51%, p=.248)

There were no differences overall for death in the delivery room or death during the hospitalization, nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. (Table 2). More CPAP infants were alive and off mechanical ventilation by day 7, ($p=0.0149$). We prospectively recorded air leaks in the first 14 days and there were no differences between the groups, and no differences for medical or surgical NEC, PDA requiring surgery, severe IVH or airleaks during the hospital stay. All infants in the Surfactant arm were intubated, compared with 83% of the CPAP infants who required intubation during their nursery course, ($p<0.0001$). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants, 7% vs13%, $p=0.0004$).

Strata Results: 24 – 25 weeks Gestation

There were significantly more non-Hispanic black infants in the CPAP group compared with the Surfactant group and no other differences noted in the DR for death, the need for compressions and epinephrine, and no difference in the mothers receipt of antenatal steroids. The other differences are shown in Table 3 (24-25 wk Strata). There was a significantly higher mortality (32% vs 24%, $p=0.0264$), and a significantly higher exposure to postnatal steroid for BPD, 21% vs 13%, $p=0.0198$) for the Surfactant infants compared with the CPAP group, with no differences for any other clinical outcomes including air leaks. As with the overall groups there were more infants alive and off mechanical ventilation at 1 week in the CPAP infants of this strata.

26-27 weeks Gestation

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There was no difference in mortality for the CPAP vs Surfactant groups, 10% vs 11%. The CPAP infants required fewer days of oxygen, 36.8 vs 46.5, p=0.0097, lesser days of mechanical ventilation, 10.7 vs 14.2, p=0.0068, and less postnatal steroids for BPD, 3% vs 8%, p=0.0027.

Discussion:

This is the first large multicenter study to prospectively compare early CPAP, with early surfactant given within an hour of life to a large group of ELBW infants. There have been many retrospective cohort reviews suggesting that early CPAP reduced the occurrence of BPD without increasing other morbidities.[20] More recent experiences also suggest that there may an increase in retinopathy of prematurity with the early use of bubble CPAP.[21] The current trial is the largest study reported to prospectively compare CPAP and Surfactant for the ELBW infant and the only study to include infants of 24 weeks gestation. In a preliminary study we found that 100% of infants of 23 weeks gestation required intubation in the DR, and thus decided that such infants would be unlikely to be successfully treated with CPAP alone following delivery.[22] Others have retrospectively reported that some of these infants can be successfully managed with early CPAP, but the majority of such infants require intubation.[23] Our study differs from the recently reported COIN trial14 in that we randomized all eligible ELBW infants of consenting families irrespective of whether they demonstrated spontaneous breathing, included infants of 24 weeks gestation, and compared the CPAP/permissively ventilated infants with infants who all received surfactant within 1 hour of birth. Our methodology of using early CPAP and a permissive ventilation strategy was a result of previous retrospective reviews of practice which demonstrated that the unit with the most success using CPAP also utilized a very permissive approach for intubation and the initiation of mechanical ventilation, and we felt that testing this complete approach would be provide a more relevant result as most units currently using early CPAP also tend to be permissive in their use of intubation. Indeed the actual study sites varied greatly in the prestudy practices with many already having adopted an early CPAP approach. All centers agreed to the protocol, and we followed all study protocol violations. The commonest problems were the failure to give surfactant within the first hour to both the Surfactant infants (n=30) and CPAP infants who were intubated (n=34).

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Our study has demonstrated that early CPAP and a permissive ventilator strategy when compared with surfactant given within 1 hour of birth is associated with a reduction in death or survival with BPD as defined by the need for oxygen at 36 weeks from 54% to 48%. These occurrences are higher than those reported for the COIN trial, 33.9% vs 38.9%, but the difference between the arms is very similar. The higher rates seen in our study no doubt reflect the inclusion of infants of 24 weeks gestation and the lack of inclusion of infants greater than 27 6/7ths weeks, as well as the requirement in the COIN trial that the infants demonstrate adequate spontaneous breathing at 5 minutes of life. Our study had more infants in our large strata (751) than any previously reported retrospective or prospective study of the use of CPAP and the 565 infants in our 24 to 25 week strata represents the largest prospective group of such immature infants to be randomized in any neonatal trial comparing respiratory outcomes.

We prospectively identified a number of safety outcomes that we chose to follow as investigators. These included the need for compressions in the delivery room, the occurrence of severe IVH, and the incidence of airleaks, initially defines as pneumothoraces but later altered to include pulmonary interstitial emphysema, pneumomediastinum and pneumopericardium. These results were provided for the total group of enrolled infants, not by study assignment, and were compared to the occurrence of these outcomes using the generic database of the Neonatal Research Network for 2002 to 2004 for infants of 24 to 27 weeks gestation preceeding the initiation of the study. The investigators agreed that as long as these occurrences were within the previous rates that there would minimal concern and the DSMB at all times had full access to all information including these occurrences by randomized group. We did not find any significant increase in these outcomes.

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From:	Cunningham, Meg
To:	Susan Hintz
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.; Yao, Qing; Newman, Jamie; Zaterka-Baxter, Kristin
Subject:	RE: Data requests, tracking, etc re: SUPPORT neuroimaging
Date:	Friday, August 28, 2009 12:27:44 PM
Attachments:	responsetoSusan.doc

Hi Susan,

Please see attached for all of our responses (in red).

Have a great weekend!
Meg

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Tuesday, August 25, 2009 1:35 AM
To: Cunningham, Meg
Cc: Rosemary Higgins; Das, Abhik; Auman, Jeanette O.; Yao, Qing; Newman, Jamie
Subject: Data requests, tracking, etc re: SUPPORT neuroimaging

Hi Meg, Qing, Jenny, Jamie, Rose, Abhik,

With the second central US reading for SUPPORT just completed, we now need to tackle the issue of what we have completed, what we have left to do, what is missing, etc. We need this to plan how the rest of the CUS readings will be done, the timeline, and analysis plans. **I would like for us to have something completed for late breakers PAS - and I think realistically we need to say all readings must be done and input by beginning of November, providing we have been inputting the central reader data as it comes in.** (And also provided we start data cleaning and plan for analysis strategy.)

In addition, thinking about how we will wrap up the neuroimaging readings and analysis has reminded me to ask a separate series of questions about the 18-22 mo follow-up and school-age follow-up.

So here it goes -

1) Characterization of CUS studies: expected, done, left to do, plans for remaining reading.

a. In order to plan how many days we need to read with Dr. Bulas and Dr. Slovis, we will need the following info:

i. How many total CUS are expected in the entire study? (All MRI01 forms should be submitted by now, so we should know this number at this point.)

ii. Are any of these "expected" CUS still not sent to RTI by the sites?

iii. How many CUS were read in the first central reading by DB, how many by TS?

iv. How many total CUS were read in the second central reading by DB, how many by

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TS?

v. How many patients have BOTH early and late CUS? How many of these have been completely read by both DB and TS?

vi. How many have COMPLETE neuroimaging (early CUS, late CUS, MRI)

b. Of course we want every CUS we can get, but the most important group for the study as a whole is the group that has all neuroimaging. So, we should be most aggressive about getting the CUS that are missing in that group.

2) Setting up more readings

a. As we discussed at the central reading, we should **move forward now with arranging separate dates for RTI to go out to Dr. Slovis and Dr. Bulas to finish up** the readings- and I think Meg may already be looking at dates for her and Amanda to vist with Dr. Bulas. I believe Julie will be going out to see Dr. Slovis? In any case, I recommend nailing down a FEW DATES NOW for the next 4 -6 weeks (even if it is a day here and a day there).

3) More data requests, but related to above questions:

a. The big spreadsheet Meg has and I want: Meg has a very nice spreadsheet with what I believe is ALL patients who were enrolled in SUPPORT Neuroimaging who have ANY CUS. Could I have an updated version of that electronically?

i. Will the "updated version" I receive be final and complete? In other words, will all the MRI01 data be in by now.

ii. Also, that spreadsheet indicates if Early or Late US and MRI were doneŠbut not whether they have been received. I really don't want to make that spreadsheet more cumbersome, so don't add columns, you can just answer 1.b above.

b. "MasterMRIFU" data sheet: Jenny Auman made a really nice spreadsheet for me with all sorts of information pertinent to the neuroimaging and follow-up issues. Jenny - could I have an updated version? **I am attaching the June 10 version just to show you which spreadsheet I mean.**

c. Pertinent to questions 1.f - looking at the June 10 version of the MasterMRIFU list, it seems that there are only 12 patients with an early CUS and a successful MRI, but NO late CUSŠthis is a group (and of course there may be more than 12 now) that we should really try to understand. As I said above, the most important group we should focus on is the group that have ALL neuroimaging, so if they are missing a late CUS but they actually have one somewhere, we should try to snag it.

4) Tracking for extended follow-up - I know a lot of questions will come up about the details of this and the $$ involved as we move toward the follow-up of this group. So here are a few questions and comments -

a. REMINDERS to sites? As you know, we did remind PI's about the 3-4 year tracking for the school age follow-up on the FU PI conference call. However, can we do something more formal - or are you already doing that? Can you - or are you already planning to - send out an email 3 months before the 3-4 year window opens to remind about the form, then again at 3 _ years IF the form is not yet completed? I know that sites don't like to be "bugged", but if they understand that tracking reimbursement is LINKED to completion of that form, it may be better tolerated.

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i. BTW, from the MasterMRIFU spreadsheet I think we have **68 or 69 subjects who have already have their window open for 3-4 year tracking! 9 or 10 patients will have that window CLOSED by the end of this month!** Are the tracking forms in on those yet?

b. $$ for tracking between 18-22 months and 3-4 years: Rose, can you tell me how much was the FINAL budgeted for the contacts between 18-22 months and 3-4 years? We had said in the original budget that it would be 2 one-hour contacts at $35/hr, but I think that was revised upward. Also, from a process perspective, when are those funds released to sites? As soon as they complete the 3-4 year tracking form? Or when the patient will reach 3-4 years IF the tracking form has been completed?

c. How will the later tracking funds will be distributed and contact attempts "verified"? In the protocol, we originally budgeted four 2 hour tracking contacts (total 8 hours of tracking contact at $35/hr) for tracking between 3-4 years and the school age follow-up visit. We now have a mechanism in place to "track the tracking" at 3-4 years. But what should we do for tracking between 3-4 and the school age visit? Just a reminder email at 5 _ years? And are we just distributing the tracking funds without "verification"?

5) Data "cleaning" and analysis:

a. Qing - we could probably start talking about starting some data clean up and setting up analyses so we can be ahead of the game.

i. I have a few ideas for cleaning up the data. For instance, we will need to look at "normal" and make sure there really are NO things marked on the form or comments made. Also, we will need to search the comments for any mention of cerebellar or cerebellum because some abnormalities in that area were not so easily categorized. Also a few other things, but I will make a list of things I am thinking about, and you can also tell me what you think.

ii. As for how we will look at the data and prelim analysis - should I put together some mock data tables?

Thanks again all! I am sure I have forgotten a lot, but that's it for now.

THANKS for all your help and great work!

Susan

--

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Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
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1) Characterization of CUS studies: expected, done, left to do, plans for remaining reading.

a. In order to plan how many days we need to read with Dr. Bulas and Dr. Slovis, we will need the following info:

i. How many total CUS are expected in the entire study? (All MRI01 forms should be submitted by now, so we should know this number at this point.)

We still have 10 missing MRI01 forms and they've been reported to the Centers as such. However, we currently have 676 patients enrolled, 652 with an Early US reported and 571 with a Late US reported.

ii. Are any of these "expected" CUS still not sent to RTI by the sites?

Yes, I am waiting on:
3 early HUS from UCSD
5 early HUS and 3 late HUS from Dallas – Nancy Miller is working to track them down
1 early and late from Houston that was a problem at the last reading, I have emailed her
1 early and late from UAB that was a problem at the last reading, I have emailed her

iii. How many CUS were read in the first central reading by DB, how many by TS?

For the first reading,

Reader Initials	TotalRead
Db	433
Ts	425

iv. How many total CUS were read in the second central reading by DB, how many by TS?

Can't do this until the forms are keyed, I anticipate the keying to take 3 weeks, however, I sent you rough numbers and I estimate:
DB=458
TS=346

v. How many patients have BOTH early and late CUS? How many of these have been completely read by both DB and TS?

Per the keyed MRI01 forms at this point (10 still pending), 568 patients have both an early and late US. The second question can't be answered until all the most recent set of MRI04 forms are keyed.

vi. How many have COMPLETE neuroimaging (early CUS, late CUS, MRI)

Per the keyed MRI01 forms at this point (10 still pending), 542 patients have all three images. There is one patient with missing codes in the MRI date, so Jenny will investigate what happened with that one.

b. Of course we want every CUS we can get, but the most important group for the study as a whole is the group that has all neuroimaging. So, we should be most aggressive about getting the CUS that are missing in that group.

2) Setting up more readings

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a. As we discussed at the central reading, we should **move forward now with arranging separate dates for RTI to go out to Dr. Slovis and Dr. Bulas to finish up** the readings- and I think Meg may already be looking at dates for her and Amanda to vist with Dr. Bulas. I believe Julie will be going out to see Dr. Slovis? In any case, I recommend nailing down a FEW DATES NOW for the next 4 -6 weeks (even if it is a day here and a day there).

Amanda and Meg will be at Children's on September 14th to read with Dorothy and hopefully finish up with her. We may need on additional 4 hour block and we will set up a second time with Dorothy.

For Tom in Detroit, we will need one longish trip out there to finish up, Meg and Julie plan to go out there October 25-27. I will also have him block a couple days in early November if needed.

3) <u>More data requests, but related to above questions</u>:
a. The big spreadsheet Meg has and I want: Meg has a very nice spreadsheet with what I believe is ALL patients who were enrolled in SUPPORT Neuroimaging who have ANY CUS. Could I have an updated version of that electronically?

We will send in a couple of weeks when it is updated.

i. Will the "updated version" I receive be final and complete? In other words, will all the MRI01 data be in by now.

We still have 10 MRI forms pending.

ii. Also, that spreadsheet indicates if Early or Late US and MRI were done but not whether they have been received. I really don't want to make that spreadsheet more cumbersome, so don't add columns, you can just answer 1.b above.

Meg will send you something shortly.

b. "MasterMRIFU" data sheet: Jenny Auman made a really nice spreadsheet for me with all sorts of information pertinent to the neuroimaging and follow-up issues. Jenny - could I have an updated version? **I am attaching the June 10 version just to show you which spreadsheet I mean.**

Jenny sent this to Susan on 8/26.

c. Pertinent to questions 1.f - looking at the June 10 version of the MasterMRIFU list, it seems that there are only 12 patients with an early CUS and a successful MRI, but NO late CUSŠthis is a group (and of course there may be more than 12 now) that we should really try to understand. As I said above, the most important group we should focus on is the group that have ALL neuroimaging, so if they are missing a late CUS but they actually have one somewhere, we should try to snag it.

Meg has queried the centers about these and will let you know when she hears back.

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4) Tracking for extended follow-up - I know a lot of questions will come up about the details of this and the $$ involved as we move toward the follow-up of this group. So here are a few questions and comments -

a. REMINDERS to sites? As you know, we did remind PI's about the 3-4 year tracking for the school age follow-up on the FU PI conference call. However, can we do something more formal - or are you already doing that? Can you - or are you already planning to - send out an email 3 months before the 3-4 year window opens to remind about the form, then again at 3 _ years IF the form is not yet completed? I know that sites don't like to be "bugged", but if they understand that tracking reimbursement is LINKED to completion of that form, it may be better tolerated.

Reminders for missing forms can be posted to the web as they are for the other protocols, we don't email them out anymore, it's too time consuming. I'll add this to the list of special edit reports. Also, Jamie sent a reminder to all PIs/coordinators concerning the SEF01 and the tracking tools for 6-7 Year Follow-up on 08/25/2009

i. BTW, from the MasterMRIFU spreadsheet I think we have **68 or 69 subjects who have already have their window open for 3-4 year tracking! 9 or 10 patients will have that window CLOSED by the end of this month!** Are the tracking forms in on those yet?

I have an MR table that shows the numbers for this, I can attach the missing forms edit to it.

b. $$ for tracking between 18-22 months and 3-4 years: Rose, can you tell me how much was the FINAL budgeted for the contacts between 18-22 months and 3-4 years? We had said in the original budget that it would be 2 one-hour contacts at $35/hr, but I think that was revised upward. Also, from a process perspective, when are those funds released to sites? As soon as they complete the 3-4 year tracking form? Or when the patient will reach 3-4 years IF the tracking form has been completed?

c. How will the later tracking funds will be distributed and contact attempts "verified"? In the protocol, we originally budgeted four 2 hour tracking contacts (total 8 hours of tracking contact at $35/hr) for tracking between 3-4 years and the school age follow-up visit. We now have a mechanism in place to "track the tracking" at 3-4 years. But what should we do for tracking between 3-4 and the school age visit? Just a reminder email at 5 _ years? And are we just distributing the tracking funds without "verification"?

5) Data "cleaning" and analysis:

a. Qing - we could probably start talking about starting some data clean up and setting up analyses so we can be ahead of the game.

i. I have a few ideas for cleaning up the data. For instance, we will need to look at "normal" and make sure there really are NO things marked on the form or comments made. Also, we will need to search the comments for any mention of

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cerebellar or cerebellum because some abnormalities in that area were not so easily categorized. Also a few other things, but I will make a list of things I am thinking about, and you can also tell me what you think.

Please make a list and send to Qing, she will look this over, add anything if needed, and you guys can get to work!

ii. As for how we will look at the data and prelim analysis - should I put together some mock data tables?

Sure, please. Mock tables do help get analysis organized. I will also look into the protocol to think about analyses. We will probably have many rounds to get the analysis finalized, so feel free to ask me anything that may come up. I am looking forward to it. -QY

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From: Sayers, Suzanne A
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; Finer, Neil
Subject: RE: SUPPORT******
Date: Friday, August 28, 2009 12:18:51 PM

Good Morning Rosemary,

I have changed the answer to the question on (b) (6) because the patient definitely was not 18 months old at the time of the exam. Sorry for the inconvenience.
Please let us know if you need us to correct anymore information. Thank you.

Respectfully,
S. Alex Sayers
Data Coordinator - Neonatology
402 Dickinson Street, Suite 1-140
San Diego, CA 92103-8774
Mail Code 8774
P: 619-543-5854
F:619-543-3812

From: Rich, Wade
Sent: Friday, August 28, 2009 7:32 AM
To: Bridge, Renee; Sayers, Suzanne A
Subject: FW: SUPPORT******

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 7:30 AM
To: Rich, Wade; Finer, Neil
Cc: mgantz@rti.org
Subject: SUPPORT******

Hi - we are missing one patient from you - Thanks for all your help

Rose

22 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.

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From: Wally Carlo, M.D.
To: Gantz, Marie; Finer, Neil; Zaterka-Baxter, Kristin; Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: RE: ROP documents
Date: Friday, August 28, 2009 12:03:29 PM
Attachments: ROP.8.28.09.doc

Dear Neil, Rosemary, Rich, Abhik, Kristin, and Marie:

Enclosed is a first draft of the oxygen saturation paper. The Introduction and Methods are complete. I have not worked on the rest of the pending results and/or interpretation of them.

See you on Wednesday.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 2:56 PM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Neil,

As far as the primary outcome is concerned, in the data I sent a positive ROP outcome is defined as when both eyes meet the criteria of vessels in zone 4=Mature for one exam or in zone 3=III for two consecutive exams. A negative ROP outcome is defined as when one or both eyes has Threshold (New Type I) ROP as recorded on the SUPP10, has ROP stage 4 or 5, or has surgery for ROP.

The reason I sent such detailed data is that we need to review the exam data for inconsistencies or "red flags" that would cause us to doubt that the data are correct. For example, if one eye has lowest zone of any vessels of 4=Mature and the other eye has ROP stage 4, we would probably want to query that site to see if a typo had been made. As I look at the data I sent you all, I can see multiple instances where there are such inconsistencies that need to be cleared up. But, I am not an expert on ROP, so I know that I will not be able to identify all potential problems on my own. I will need other eyes to review the data so that we can put together queries to send the centers.

Thanks, everyone, for your help in this. I know it's a lot to look at, but it will help us ensure that our primary outcome data are as clean as possible.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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828-254-6255

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, August 27, 2009 3:42 PM
To: Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Hi Marie
We are looking at the crosstabs and will send a final answer in an hour or so. Overall we should resolve any discrepancies but for timing etc – unless the difference indicates that the intervention was done as per protocol or not, then such discrepancies are not worth resolving
The ROP data is obviously based on Dales very detailed input. However, lets look at how we are defining ROP – either threshold or surgery –
I assume that for any child, a single eye involvement is sufficient to meet this primary and concordance between the eyes is of interest but not for the primary.
The definition of the Threshold ROP is as follows:
Threshold (New Type I) ROP
Threshold (New Type I) ROP is defined as:
• In Zone II: plus disease with stage 2 or stage 3
• In Zone I: plus disease with any stage ROP, or stage 3 without plus disease
I can't see where it was said or not but are you working on the assumption that an infant has ROP if they meet the criteria or had surgery on any eye or are you looking at both eyes. For me, it would be any eye in a child that meets the definition of Threshold, whether the other eye meets this or not and the same for surgery.
Much of the data that you sending I believe is for more secondary outcomes to look at more detail than is needed or wanted for the Primary. Is this also your understanding of this issue?
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 11:37 AM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: ROP documents

Hi all,

Please find attached four ROP documents for your review (described below). Before we do the ROP analysis, we will need to clean the ROP data as we have been doing for BPD. This will likely involve sending out a batch of queries for the centers to resolve inconsistencies within and between forms. As I am less familiar with ROP than I am with the BPD outcomes, I will need your help to identify inconsistencies that need to be resolved. The attached documents were created in order to facilitate that process. Perhaps we can review them together during our meeting on Monday.

1) **SUPP10 ROP cross-tabs (all exams) 8-27-09.rtf** – This document contains cross-tabulations of ROP data for all exams entered on the SUPP10. The purpose of this document is to help identify any inconsistent data within the exams.
2) **Current and previous exam results by ROP reason 8-27-09.rtf** – For all infants with a final

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ROP determination, selected data from the current exam (from which the ROP determination was made) and the previous exam for the infant are presented. Additional information included are the estimated PMA at the time of the current exam and the number of days between the current and previous exam. The purpose of this document is to help identify cases where the change in ROP data between exams seems unreasonable for the amount of time that elapsed between the exams.

3) **Cases where ROP status changed per SUPP10 8-27-09.rtf** – This document lists data from each ROP exam for infants whose final ROP status appears to have changed over time (final status was positive but changed to negative at a subsequent exam or vice versa). The purpose of this document is to determine whether or not the changes in status seem reasonable.
4) **ROP on NG03 vs SUPP10 8-27-09.rtf** – This document contains cross-tabulations of similar data fields on the NG03 and SUPP10. Note that only SUPP10 exams that occurred by the date of NG03 status are included in this comparison. Because ROP exam dates are not entered on the NG03, and it is therefore not clear precisely which exams were consulted when the NG03 data were entered, it may be difficult to compare the data on these two forms.

Neil and Wade, have you had a chance to look over the proposed cross-form queries I sent you on 8/18? As these queries involve many important data elements, including treatment variables like intubation/surfactant and outcomes like air leaks and IVH, we need to have these inconsistencies resolved before we finalize the SUPPORT manuscripts. If at all possible, I would like to send these queries to the centers by the end of next week. As I told everyone when we planned the analysis meeting, I will be out of town September 5-20, so it would be nice if the centers could be working on the queries during that time.

For the meeting on Monday, I will have my analysis datasets for BPD, ROP and other outcomes available for review. Please let me know if there is anything else of high-priority for me to prepare for Monday. Time is obviously limited, but I will try to accommodate.

I look forward to reviewing the SUPPORT data with you next week.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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1st draft 8/28/09
10:30 a.m.

The Effect of Higher Versus Lower Oxygen Saturation Targeting on Retinopathy of Prematurity and Mortality in Very Premature Infants

Corresponding author and reprints:

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Word count:

Abstract:

Manuscript:

Running head: oxygen saturation and retinopathy of prematurity

Key words: prematurity, extremely low birth weight infant, neonatal mortality, oxygen toxicity

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ABSTRACT

Background

The incidence of retinopathy increases with exposure to high levels of oxygenation in premature infants but the range of oxygen saturations that reduce adverse outcomes is not known.

Methods

We randomly assigned at birth 1310 infants of 24 to 27 weeks gestation to oxygen saturation targets of 85 to 89% or 91 to 95%. The primary outcome was a composite of threshold retinopathy of prematurity, eye surgery for retinopathy, and/or death.

Results

Conclusions

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INTRODUCTION

Retinopathy of prematurity remains an important cause of blindness and other visual disabilities among prematurely born infants. The incidence of retinopathy of prematurity is increased with exposure to high levels of oxygenation in premature infants. Oxygen saturation levels previously thought to be in the upper limits of normal increase the risk of retinopathy of prematurity.[1, 2, 3] Oxygen toxicity may also increase the risk of mortality[4,5], bronchopulmonary dysplasia[6,7], and other morbidities. While data from prospective observational and retrospective studies suggest that maintenance of oxygenation at lower ranges may decrease the incidence of retinopathy of prematurity, there is no conclusive evidence regarding the oxygenation levels that reduce retinopathy of prematurity without an increase in adverse effects.

We conducted a 2 x 2 factorial-design multicenter randomized trial of oxygen saturation targeting, testing the effect of a lower oxygen saturation range (85-89%) as compared to a higher oxygen saturation range (91-95%) on the incidence of threshold retinopathy of prematurity and/or need for surgical eye intervention or death among infants of 24 to 27 weeks gestational age at birth. The factorial design allowed comparing prophylactic/early surfactant versus continuous positive airway pressure, thus, controlling for the approach to ventilatory support.

METHODS

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The institutional review boards at all Neonatal Research Network clinical centers and Research Triangle International approved the trial. Written informed consent was obtained from the parent or guardian of each participant.

Patients

Infants of $24^{0/7}$ to $27^{6/7}$ weeks without a decision to forgo support were eligible for enrollment at birth. Exclusion criteria were outborn infants and major congenital anomalies. Multiples were randomized to the same arm of the trial.

Enrollment and treatment

Infants were stratified by gestational age ($24^{0/7}$ to $25^{6/7}$ weeks or $26^{0/7}$ to $27^{6/7}$ weeks) and by center. Infants were randomly assigned by means of double-sealed envelopes to oxygen saturation targeting of 85 to 89% or 91 to 95% with masking using electronically-altered pulse oximeters with output display of 88 to 92% for these oxygen ranges, an offset of 3% as previously used to separate oxygen saturations in premature infants.[8] They were also randomly assigned to respiratory support using either prophylactic/early surfactant with conventional ventilation management or continuous positive airway pressure with permissive ventilation management. The oxygen saturation values displayed reverted to actual values when less than 85% or greater than 95%. Saturation targeting was initiated immediately following admission and no later than two hours after admission. Oxygen saturation targeting with the altered pulse oximetry was continued as long as the infant remained on room air and off the ventilator/continuous positive airway pressure for 72 hours until 36 weeks post-menstrual age. Targeting of saturation was performed by the clinicians, not by the research staff.

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Assessments

Research nurses recorded all data using standardized definitions. Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy [ETROP] Cooperative Group[9]) was coded if any of the following four findings were present up to 52 weeks post-menstrual age:

If in Zone 1: Stage 3 retinopathy of prematurity, even without plus disease
Plus disease with any stage retinopathy of prematurity

If in Zone II: Plus disease with stage 2 retinopathy of prematurity
Plus disease with stage 3 retinopathy of prematurity

Surgical intervention included laser therapy, cryotherapy, laser/cryotherapy, scleral buckle, and vitrectomy. Death was coded up to 36 weeks post-menstrual age. Secondary outcomes included each of the individual outcomes above and predefined clinical diagnoses and potential adverse events.

Statistical analysis

The primary analysis of this factorial trial was a logistic regression analysis of the percentages of infants in each group (lower versus higher oxygen saturations) who developed the primary outcome. An absolute difference of 10% between the two treatment groups was considered clinically important. To detect the difference, we planned to enroll 1310 infants for 80% power and a baseline rate of 45% of death/threshold retinopathy/surgery. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted by the staff at the data center. A two-sided P value of less than 0.05 was considered to statistically significant. Analyses did not include adjustment for

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multiple comparisons. An independent data safety monitoring committee reviewed the interim results, including those concerning adverse outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring.

RESULTS

DISCUSSION

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REFERENCES

1.

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From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ******SUPPORT OUCOMES*******
Date: Friday, August 28, 2009 10:32:44 AM

Rose
Will be done today
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

-----Original Message-----
From: Bara, Rebecca
Sent: Friday, August 28, 2009 10:17 AM
To: Shankaran, Seetha; Sood, Beena
Subject: RE: ******SUPPORT OUCOMES*******

The remainders will be keyed today. Thank you for your patience.

Becky

From: Shankaran, Seetha
Sent: Friday, August 28, 2009 10:06 AM
To: Sood, Beena; Bara, Rebecca
Subject: FW: ******SUPPORT OUCOMES*******

Beena and Becky
Lets do this ASAP---results were personated at PI call earlier this week
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 28, 2009 9:55 AM
To: Shankaran, Seetha; bsood@wayne.med.edu; Becky bara
Cc: mganz@rti.org

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Subject: ******SUPPORT OUCOMES*******

Hi,

We urgently need final SUPPORT outcomes.

Please enter tham asap. Thanks for all the help!!

CENTER
NETWORK ROP_message

5 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.
5 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER NETWORK FU_message
5 (b) (6) FU window has closed but NF05 and NF09a have not been completed.
5 (b) (6) FU marked as complete (per NF10/SF10) but NF05 has not been completed.
5 (b) (6) FU window has closed but NF09a has not been completed.

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From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; scrosby@peds.uab.edu
Cc: mgantz@rti.org
Subject: RE: ****SUPPORT******
Date: Friday, August 28, 2009 10:28:29 AM

We're on it
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 8/28/2009 9:19 AM
To: Wally Carlo, M.D.; Monica Collins; scrosby@peds.uab.edu
Cc: mgantz@rti.org
Subject: ****SUPPORT******

Hi

We are missing a few SUPPORT outcomes. Thanks for all your help!!
Rose

16 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.
16 (b) (6) The patient is within their Fol-up window and final ROP status has not been reported.
16 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: alaptook@WIHRI.org; bvohr@wihri.org; Angelita Hensman
Cc: mgantz@rti.org
Subject: ***SUPPORT*****
Date: Friday, August 28, 2009 10:15:17 AM

Hi,
We are missing a few support outcomes - thanks for all your help

Rose

14	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
CENTER	NETWORK	BPD_message
14	(b) (6)	NG07 section C is filled out but the PHY01 is also expected because this is a SUPPORT infant.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Das, Abhik
Subject: Missing outcomes for SUPPORT
Date: Thursday, August 27, 2009 8:42:41 PM
Attachments: SUPPORT infants with missing ROP 08-27-09.rtf
Infants with missing outcomes 08-27-09.xls

Attached is the list of infants who are missing SUPPORT outcomes this week as well as an update on infants still missing the ROP outcome.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Reasons ROP is missing

The FREQ Procedure

Reason for no ROP classification				
noropreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1=Infant withdrawn	4	3.23	4	3.23
1=Estimated PMA <55 weeks	5	4.03	9	7.26
2=Lowest zone of any vessels is I at last exam	2	1.61	11	8.87
3=Lowest zone of any vessels is II at last exam	56	45.16	67	54.03
4=Lowest zone of any vessels is III for one exam	56	45.16	123	99.19
5=PMA>=55 weeks but no ROP exams entered	1	0.81	124	100.00

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=2=Lowest zone of any vessels is I at last exam

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
1	33	3	P	1	P	195	Y	N	3=Closed
2	47	1	2	1	2	241	Y	N	3=Closed

Reason for no ROP classification=3=Lowest zone of any vessels is II at last exam

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
3	36	2	2	2	2	56			1=Not open yet
4	38	2	2	2	2	58	Y		1=Not open yet
5	38	2	2	2	2	59			1=Not open yet
6	33	2	1	2	1	61			1=Not open yet
7	37	2	2	2	2	61			1=Not open yet
8	35	2	2	2	2	64			1=Not open yet
9	49	2	2	2	2	65		Y	.
10	37	2	2	2	2	70	Y		1=Not open yet
11	33	2	.	2	.	71			1=Not open yet
12	39	2	2	2	2	73	Y		1=Not open yet
13	41	2	2	2	2	77	Y		1=Not open yet
14	42	3	2	2	2	78			1=Not open yet
15	33	2	2	2	2	79			1=Not open yet
16	35	2	2	2	2	81			1=Not open yet
17	39	2	2	2	2	81	Y		1=Not open yet
18	37	2	2	2	2	85			1=Not open yet
19	35	2	2	2	2	86			1=Not open yet
20	34	2	2	2	2	89			1=Not open yet
21	38	2	2	2	2	90			1=Not open yet
22	36	2	2	2	2	97			1=Not open yet
23	38	2	1	2	1	102	Y		1=Not open yet
24	49	2	3	2	3	107	Y		1=Not open yet
25	43	2	2	2	2	109			1=Not open yet
26	50	2	2	2	2	109	Y		1=Not open yet
27	44	2	2	2	2	109	Y		1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels - previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status (Y/N) at FU at 55 weeks PMA	Threshold ROP status obtained after	FU window
28	42	2	2	2	2	109		N	1=Not open yet
29	33	2	2	2	2	111	Y		1=Not open yet
30	38	2	2	2	2	112	Y		1=Not open yet
31	36	2	2	2	2	113			1=Not open yet
32	41	2	2	2	2	117	Y		1=Not open yet
33	38	2	2	2	2	119			2=Open now
34	36	2	2	2	2	121	Y		2=Open now
35	32	2	1	2	1	123		N	2=Open now
36	38	2	2	2	2	125	Y		2=Open now
37	36	2	2	2	2	126			2=Open now
38	65	2	2	2	2	126	Y	N	2=Open now
39	41	2	2	2	2	132			2=Open now
40	77	2	2	2	2	134		N	2=Open now
41	34	2	2	2	2	135	Y	N	2=Open now
42	105	2	2	2	2	138		N	3=Closed
43	46	2	2	2	2	138		N	3=Closed
44	33	2	.	2	.	143	Y	N	3=Closed
45	44	2	2	2	2	145	Y		3=Closed
46	71	2	2	2	2	149		N	3=Closed
47	85	2	2	2	2	152	Y	N	3=Closed
48	55	9	2	9	2	155	Y	N	3=Closed
49	39	2	2	2	2	155			3=Closed
50	44	2	2	2	2	191	Y	N	3=Closed
51	43	2	2	2	2	202			3=Closed
52	37	2	2	2	2	204	Y	N	3=Closed
53	94	2	2	2	2	226	Y	N	3=Closed
54	34	2	2	2	2	226	Y	N	3=Closed
55	78	2	2	2	2	240	Y	N	3=Closed
56	35	2	2	2	2	247	Y	N	3=Closed
57	64	2	2	2	2	249	Y	N	3=Closed
58	36	2	2	2	2	249		N	3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=4=Lowest zone of any vessels is III for one exam

Obs	Estimated PMA of last ROP exam (wks)	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
59	42	3	2	3	2	55		N	1=Not open yet
60	50	3	2	3	2	64			1=Not open yet
61	37	3	.	3	.	66			1=Not open yet
62	38	3	2	3	2	67	Y		1=Not open yet
63	34	3	2	3	2	68	Y		1=Not open yet
64	36	3	.	3	.	69			1=Not open yet
65	38	3	2	3	2	70	Y		1=Not open yet
66	39	3	2	3	2	74	Y		1=Not open yet
67	40	3	2	3	2	78	Y		1=Not open yet
68	36	3	2	3	2	79	Y		1=Not open yet
69	37	3	2	3	2	81	Y		1=Not open yet
70	35	3	2	3	2	83			1=Not open yet
71	36	3	2	3	2	85	Y		1=Not open yet
72	41	3	2	3	2	89	Y		1=Not open yet
73	35	3	2	3	2	91	Y		1=Not open yet
74	41	3	2	3	2	94	Y		1=Not open yet
75	40	3	2	3	2	94	Y		1=Not open yet
76	36	3	2	3	2	97	Y		1=Not open yet
77	37	3	2	3	2	98	Y		1=Not open yet
78	39	3	2	3	2	99	Y		1=Not open yet
79	38	3	2	3	2	100			1=Not open yet
80	35	3	2	3	2	101	Y		1=Not open yet
81	38	3	2	3	2	102			1=Not open yet
82	39	3	2	3	2	105	Y		1=Not open yet
83	33	3	2	3	2	110			1=Not open yet
84	40	3	2	3	2	110	Y		1=Not open yet
85	34	3	2	3	2	111	Y		1=Not open yet
86	36	3	2	3	2	112			1=Not open yet
87	39	3	2	3	2	112			1=Not open yet
88	41	3	2	3	2	114	Y		1=Not open yet
89	34	3	2	3	2	115	Y	?	1=Not open yet
90	37	3	2	3	2	117	Y		1=Not open yet
91	36	3	2	3	2	126			2=Open now
92	48	3	2	3	2	127			2=Open now

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left lowest zone for any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
93	44	3	2	3	2	136	Y		2=Open now
94	44	3	2	3	2	140			3=Closed
95	35	3	2	3	2	145	Y		3=Closed
96	37	3	2	3	2	155	Y	N	3=Closed
97	39	3	2	3	2	155			3=Closed
98	46	3	2	3	2	167	Y	N	3=Closed
99	36	3	2	4	2	168	Y		3=Closed
100	38	3	2	3	2	179	Y	N	3=Closed
101	44	3	2	3	2	222	Y		3=Closed
102	37	3	2	3	2	228	Y	N	3=Closed
103	55	3	2	3	2	229	Y		3=Closed
104	34	3	2	3	3	231		N	3=Closed
105	32	3	.	3	.	233	Y	N	3=Closed
106	33	3	P	3	P	235	Y	N	3=Closed
107	36	3	2	3	2	243	Y	N	3=Closed
108	39	3	2	3	2	243	Y	N	3=Closed
109	33	3	P	3	P	245	Y	N	3=Closed
110	34	3	2	3	2	247	Y	N	3=Closed
111	86	3	2	3	2	247	Y	N	3=Closed
112	39	3	2	3	2	248	Y	N	3=Closed
113	88	3	2	3	2	253	Y	N	3=Closed
114	37	3	2	3	2	257	Y	N	3=Closed

Reason for no ROP classification=5=PMA>=55 weeks but no ROP exams entered

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
115	.	.	.	.	.	56			1=Not open yet

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Missing_FU

CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
5	[redacted]	FU marked as complete (per NF10/SF10) but NF05 has not been completed.
5	[redacted]	FU window has closed but NF09a has not been completed.
9	[redacted]	FU window has closed but NF05 and NF09a have not been completed.
9	[redacted]	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
9	[redacted]	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
12	[redacted]	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.
12	[redacted]	FU marked as complete (per NF10/SF10) but NF05 has not been completed.
18	[redacted]	FU window has closed but NF05 and NF09a have not been completed.

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From: Finer, Neil
To: "Gantz, Marie"; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents
Date: Thursday, August 27, 2009 5:01:13 PM

Hi Marie
Thanks for going over these Tables with me. Marie and I reviewed the discrepancies that she identified and we defined situations where a further query would be appropriate. We also reviewed the Table: Cases where ROP status changed and reviewed each one of these. Marie will query those cases that we identified.
I suggested the following as grounds for asking for further information
1. Any case where the individual eyes differed by more than 2 stages/grades
2. Any case where the ROP was diagnosed as Stage 4 or 5 with NO antecedent stages or threshold or surgery
3. Any case where the surgery was only performed in 1 eye. The usual experience is that such discrepancies occur in 10% or less of cases and Marie thinks that overall we have about 120 cases.
I hope this helps.
Thanks again Marie
Neil

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Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 12:56 PM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Neil,

As far as the primary outcome is concerned, in the data I sent a positive ROP outcome is defined as when both eyes meet the criteria of vessels in zone 4=Mature for one exam or in zone 3=III for two consecutive exams. A negative ROP outcome is defined as when one or both eyes has Threshold (New Type I) ROP as recorded on the SUPP10, has ROP stage 4 or 5, or has surgery for ROP.

The reason I sent such detailed data is that we need to review the exam data for inconsistencies or "red flags" that would cause us to doubt that the data are correct. For example, if one eye has lowest zone of any vessels of 4=Mature and the other eye has ROP stage 4, we would probably want to query that site to see if a typo had been made. As I look at the data I sent you all, I can see multiple instances where there are such inconsistencies that need to be cleared up. But, I am not an expert on ROP, so I know that I will not be able to identify all potential problems on my own. I will need other eyes to review the data so that we can put together queries to send the centers.

Thanks, everyone, for your help in this. I know it's a lot to look at, but it will help us ensure that our primary outcome data are as clean as possible.

Marie

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Marie Gantz, Ph.D.
Research Statistician
RTI International
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828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, August 27, 2009 3:42 PM
To: Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Hi Marie
We are looking at the crosstabs and will send a final answer in an hour or so. Overall we should resolve any discrepancies but for timing etc – unless the difference indicates that the intervention was done as per protocol or not, then such discrepancies are not worth resolving
The ROP data is obviously based on Dales very detailed input. However, lets look at how we are defining ROP – either threshold or surgery –
I assume that for any child, a single eye involvement is sufficient to meet this primary and concordance between the eyes is of interest but not for the primary.
The definition of the Threshold ROP is as follows:
Threshold (New Type I) ROP
Threshold (New Type I) ROP is defined as:
• In Zone II: plus disease with stage 2 or stage 3
• In Zone I: plus disease with any stage ROP, or stage 3 without plus disease
I can't see where it was said or not but are you working on the assumption that an infant has ROP if they meet the criteria or had surgery on any eye or are you looking at both eyes. For me, it would be any eye in a child that meets the definition of Threshold, whether the other eye meets this or not and the same for surgery.
Much of the data that you sending I believe is for more secondary outcomes to look at more detail than is needed or wanted for the Primary. Is this also your understanding of this issue?
Neil

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 11:37 AM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: ROP documents

Hi all,

Please find attached four ROP documents for your review (described below). Before we do the ROP analysis, we will need to clean the ROP data as we have been doing for BPD. This will likely involve sending out a batch of queries for the centers to resolve inconsistencies within and between forms. As I am less familiar with ROP than I am with the BPD outcomes, I will need your help to identify

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inconsistencies that need to be resolved. The attached documents were created in order to facilitate that process. Perhaps we can review them together during our meeting on Monday.

1) **SUPP10 ROP cross-tabs (all exams) 8-27-09.rtf** – This document contains cross-tabulations of ROP data for all exams entered on the SUPP10. The purpose of this document is to help identify any inconsistent data within the exams.
2) **Current and previous exam results by ROP reason 8-27-09.rtf** – For all infants with a final ROP determination, selected data from the current exam (from which the ROP determination was made) and the previous exam for the infant are presented. Additional information included are the estimated PMA at the time of the current exam and the number of days between the current and previous exam. The purpose of this document is to help identify cases where the change in ROP data between exams seems unreasonable for the amount of time that elapsed between the exams.
3) **Cases where ROP status changed per SUPP10 8-27-09.rtf** – This document lists data from each ROP exam for infants whose final ROP status appears to have changed over time (final status was positive but changed to negative at a subsequent exam or vice versa). The purpose of this document is to determine whether or not the changes in status seem reasonable.
4) **ROP on NG03 vs SUPP10 8-27-09.rtf** – This document contains cross-tabulations of similar data fields on the NG03 and SUPP10. Note that only SUPP10 exams that occurred by the date of NG03 status are included in this comparison. Because ROP exam dates are not entered on the NG03, and it is therefore not clear precisely which exams were consulted when the NG03 data were entered, it may be difficult to compare the data on these two forms.

Neil and Wade, have you had a chance to look over the proposed cross-form queries I sent you on 8/18? As these queries involve many important data elements, including treatment variables like intubation/surfactant and outcomes like air leaks and IVH, we need to have these inconsistencies resolved before we finalize the SUPPORT manuscripts. If at all possible, I would like to send these queries to the centers by the end of next week. As I told everyone when we planned the analysis meeting, I will be out of town September 5-20, so it would be nice if the centers could be working on the queries during that time.

For the meeting on Monday, I will have my analysis datasets for BPD, ROP and other outcomes available for review. Please let me know if there is anything else of high-priority for me to prepare for Monday. Time is obviously limited, but I will try to accommodate.

I look forward to reviewing the SUPPORT data with you next week.

Thanks,
Marie

Marie Gantz, Ph.D.
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828-254-6255

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From: Wally Carlo, M.D.
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents
Date: Thursday, August 27, 2009 5:00:05 PM

I meant to say that I agree with Neil that at this time this should only bog us down if the issue is related to the primary outcome.

Sorry that I was not clear because of trying to be brief.

See you on Monday!!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Wally Carlo, M.D.
Sent: Thursday, August 27, 2009 3:58 PM
To: Finer, Neil; Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Hi Neil:

Absolutely. This is critical for the primary outcome.

Wally

Wally Carlo, M.D.
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Director, Newborn Nurseries
619 South 20th Street
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, August 27, 2009 2:49 PM
To: Wally Carlo, M.D.; Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

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HI Wally
I am OK with this but I do not want us to get bogged down in what appears to be a lot of data for a secondary regarding detailed yery diagnoses and concordance. We need to focus on the occurrence of the primary outcome and spend time looking at such data that is unclear. The ability to make the diagnosis of ROP should be reasonably transparent, albeit there will be infants without the exam at the time etc.
Rose can we see if Dale is available for an hour on Monday afternoon so that we could engage her in such a discussion?
Thanks
Neil

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, August 27, 2009 12:11 PM
To: Gantz, Marie; Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Thanks, Marie.

In contrast to Marie, I am really unfamiliar with all the details of the ROP diagnosis. Rose is an expert on ROP. I think we need to plan to be able to consult Dale. Maybe we should check out availability for a conf call with Dale while we are in DC on Monday (just in case it is needed).

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 1:37 PM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: ROP documents

Hi all,

Please find attached four ROP documents for your review (described below). Before we do the ROP

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analysis, we will need to clean the ROP data as we have been doing for BPD. This will likely involve sending out a batch of queries for the centers to resolve inconsistencies within and between forms. As I am less familiar with ROP than I am with the BPD outcomes, I will need your help to identify inconsistencies that need to be resolved. The attached documents were created in order to facilitate that process. Perhaps we can review them together during our meeting on Monday.

1) **SUPP10 ROP cross-tabs (all exams) 8-27-09.rtf** – This document contains cross-tabulations of ROP data for all exams entered on the SUPP10. The purpose of this document is to help identify any inconsistent data within the exams.
2) **Current and previous exam results by ROP reason 8-27-09.rtf** – For all infants with a final ROP determination, selected data from the current exam (from which the ROP determination was made) and the previous exam for the infant are presented. Additional information included are the estimated PMA at the time of the current exam and the number of days between the current and previous exam. The purpose of this document is to help identify cases where the change in ROP data between exams seems unreasonable for the amount of time that elapsed between the exams.
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4) **ROP on NG03 vs SUPP10 8-27-09.rtf** – This document contains cross-tabulations of similar data fields on the NG03 and SUPP10. Note that only SUPP10 exams that occurred by the date of NG03 status are included in this comparison. Because ROP exam dates are not entered on the NG03, and it is therefore not clear precisely which exams were consulted when the NG03 data were entered, it may be difficult to compare the data on these two forms.

Neil and Wade, have you had a chance to look over the proposed cross-form queries I sent you on 8/18? As these queries involve many important data elements, including treatment variables like intubation/surfactant and outcomes like air leaks and IVH, we need to have these inconsistencies resolved before we finalize the SUPPORT manuscripts. If at all possible, I would like to send these queries to the centers by the end of next week. As I told everyone when we planned the analysis meeting, I will be out of town September 5-20, so it would be nice if the centers could be working on the queries during that time.

For the meeting on Monday, I will have my analysis datasets for BPD, ROP and other outcomes available for review. Please let me know if there is anything else of high-priority for me to prepare for Monday. Time is obviously limited, but I will try to accommodate.

I look forward to reviewing the SUPPORT data with you next week.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Wally Carlo, M.D.
To: Gantz, Marie; Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents
Date: Thursday, August 27, 2009 4:50:24 PM

Marie:
This is most thoughtful and useful.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 2:56 PM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Neil,

As far as the primary outcome is concerned, in the data I sent a positive ROP outcome is defined as when both eyes meet the criteria of vessels in zone 4=Mature for one exam or in zone 3=III for two consecutive exams. A negative ROP outcome is defined as when one or both eyes has Threshold (New Type I) ROP as recorded on the SUPP10, has ROP stage 4 or 5, or has surgery for ROP.

The reason I sent such detailed data is that we need to review the exam data for inconsistencies or "red flags" that would cause us to doubt that the data are correct. For example, if one eye has lowest zone of any vessels of 4=Mature and the other eye has ROP stage 4, we would probably want to query that site to see if a typo had been made. As I look at the data I sent you all, I can see multiple instances where there are such inconsistencies that need to be cleared up. But, I am not an expert on ROP, so I know that I will not be able to identify all potential problems on my own. I will need other eyes to review the data so that we can put together queries to send the centers.

Thanks, everyone, for your help in this. I know it's a lot to look at, but it will help us ensure that our primary outcome data are as clean as possible.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]

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Sent: Thursday, August 27, 2009 3:42 PM
To: Gantz, Marie; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: ROP documents

Hi Marie
We are looking at the crosstabs and will send a final answer in an hour or so. Overall we should resolve any discrepancies but for timing etc – unless the difference indicates that the intervention was done as per protocol or not, then such discrepancies are not worth resolving
The ROP data is obviously based on Dales very detailed input. However, lets look at how we are defining ROP – either threshold or surgery –
I assume that for any child, a single eye involvement is sufficient to meet this primary and concordance between the eyes is of interest but not for the primary.
The definition of the Threshold ROP is as follows:
Threshold (New Type I) ROP
Threshold (New Type I) ROP is defined as:
• In Zone II: plus disease with stage 2 or stage 3
• In Zone I: plus disease with any stage ROP, or stage 3 without plus disease
I can't see where it was said or not but are you working on the assumption that an infant has ROP if they meet the criteria or had surgery on any eye or are you looking at both eyes. For me, it would be any eye in a child that meets the definition of Threshold, whether the other eye meets this or not and the same for surgery.
Much of the data that you sending I believe is for more secondary outcomes to look at more detail than is needed or wanted for the Primary. Is this also your understanding of this issue?
Neil

Neil N. Finer, M.D.
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Director, Division of Neonatal-Perinatal Medicine
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, August 27, 2009 11:37 AM
To: Finer, Neil; wacarlo@uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Das, Abhik; Zaterka-Baxter, Kristin
Subject: ROP documents

Hi all,

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are the estimated PMA at the time of the current exam and the number of days between the current and previous exam. The purpose of this document is to help identify cases where the change in ROP data between exams seems unreasonable for the amount of time that elapsed between the exams.

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Neil and Wade, have you had a chance to look over the proposed cross-form queries I sent you on 8/18? As these queries involve many important data elements, including treatment variables like intubation/surfactant and outcomes like air leaks and IVH, we need to have these inconsistencies resolved before we finalize the SUPPORT manuscripts. If at all possible, I would like to send these queries to the centers by the end of next week. As I told everyone when we planned the analysis meeting, I will be out of town September 5-20, so it would be nice if the centers could be working on the queries during that time.

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Subject:	ROP documents
Date:	Thursday, August 27, 2009 2:37:16 PM
Attachments:	SUPP10 ROP cross-tabs (all exams) 8-27-09.rtf Current and previous exam results by ROP reason 8-27-09.rtf Cases where ROP status changed per SUPP10 8-27-09.rtf ROP on NG03 vs SUPP10 8-27-09.rtf

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Marie

Marie Gantz, Ph.D.

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Research Statistician
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The FREQ Procedure

Table of ropleftreason by ropleft				
ropleftreason(Reason for ROP determination in left eye)	ropleft(ROP left eye)			
Frequency	.	Y	N	Total
.	5258	0	0	5258
Threshold (Type I) ROP	0	134	0	134
ROP surgery	0	194	0	194
ROP stage 4 or 5	0	3	0	3
Lowest zone = mature	0	0	624	624
Lowest zone = III for consecutive exams	0	0	560	560
Avastin	0	3	0	3
Total	5258	334	1184	6776

Table of roprightreason by ropright				
roprightreason(Reason for ROP determination in right eye)	ropright(ROP right eye)			
Frequency	.	Y	N	Total
.	5246	0	0	5246
Threshold (Type I) ROP	0	133	0	133
ROP surgery	0	211	0	211
ROP stage 4 or 5	0	7	0	7
Lowest zone = mature	0	0	621	621
Lowest zone = III for consecutive exams	0	0	556	556
Avastin	0	2	0	2
Total	5246	353	1177	6776

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ROP reasons in left vs. right eye

The FREQ Procedure

Table of ropleftreason by roprightreason

ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)							
Frequency	.	Threshold (Type I) ROP	ROP surgery	ROP stage 4 or 5	Lowest zone = mature	Lowest zone = III for consecutive exams	Avastin	Total
.	5200	12	13	0	5	28	0	5258
Threshold (Type I) ROP	8	117	9	0	0	0	0	134
ROP surgery	1	4	187	0	2	0	0	194
ROP stage 4 or 5	0	0	0	3	0	0	0	3
Lowest zone = mature	8	0	1	4	596	15	0	624
Lowest zone = III for consecutive exams	29	0	0	0	18	513	0	560
Avastin	0	0	1	0	0	0	2	3
Total	5246	133	211	7	621	556	2	6776

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Lowest zone of any vessels vs. highest stage (in lowest any zone)

The FREQ Procedure

Table of SP10LHLZ by SP10LLWZ									
SP10LHLZ(Left-Highest stage in lowest zone)	SP10LLWZ(Left-lowest zone of any vessels)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	19	0	21	6	5	0	6	57
0=No ROP	0	17	226	1628	685	615	1	5	3177
1=Stage 1	0	0	40	1014	370	0	0	0	1424
2=Stage 2	0	0	48	1254	139	3	0	0	1444
3=Stage 3	0	1	44	410	32	0	1	0	488
4=Stage 4a or 4b	0	0	0	0	2	1	0	0	3
5=Stage 5	0	0	0	0	0	0	1	0	1
6=Post laser/cryo (do not use stages)	0	2	8	33	2	0	95	8	148
9=Old scars, but no active ROP	0	0	0	7	16	2	3	0	28
Total	6	39	366	4367	1252	626	101	19	6776

Table of SP10LHAZ by SP10LLWZ									
SP10LHAZ(Left-Highest stage in any zone)	SP10LLWZ(Left-lowest zone of any vessels)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	19	0	18	6	5	0	6	54
0=No ROP	0	17	228	1639	686	615	1	5	3191
1=Stage 1	0	0	37	1016	370	0	0	0	1423
2=Stage 2	0	0	45	1228	138	3	0	0	1414
3=Stage 3	0	1	48	422	32	0	1	0	504
4=Stage 4a or 4b	0	0	0	0	2	1	0	0	3
5=Stage 5	0	0	0	0	0	0	1	0	1
6=Post laser/cryo (do not use stages)	0	2	8	37	2	0	95	8	152
9=Old scars, but no active ROP	0	0	0	7	16	2	3	0	28
Total	6	39	366	4367	1252	626	101	19	6776

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Lowest zone of any vessels vs. highest stage (in lowest any zone)

The FREQ Procedure

Table of SP10RHLZ by SP10RLWZ									
SP10RHLZ(Right-Highest stage in lowest zone)	SP10RLWZ(Right-lowest zone of any vessels)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	17	1	19	6	4	0	7	54
0=No ROP	0	17	230	1642	707	610	1	7	3214
1=Stage 1	0	0	42	1014	322	2	0	0	1380
2=Stage 2	0	0	61	1238	148	2	0	0	1449
3=Stage 3	0	1	50	377	35	0	1	0	464
4=Stage 4a or 4b	0	0	0	4	2	1	0	0	7
5=Stage 5	0	0	0	0	0	0	1	0	1
6=Post laser/cryo (do not use stages)	0	2	11	34	1	0	108	8	164
9=Old scars, but no active ROP	0	0	0	7	24	3	3	0	37
Total	6	37	395	4335	1245	622	114	22	6776

Table of SP10RHAZ by SP10RLWZ									
SP10RHAZ(Right-Highest stage in any zone)	SP10RLWZ(Right-lowest zone of any vessels)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	17	1	16	6	4	0	7	51
0=No ROP	0	17	237	1662	707	611	1	8	3243
1=Stage 1	0	0	41	1009	323	1	0	0	1374
2=Stage 2	0	0	55	1215	148	2	0	0	1420
3=Stage 3	0	1	50	388	34	0	1	0	474
4=Stage 4a or 4b	0	0	0	0	2	1	0	0	3
5=Stage 5	0	0	0	0	0	0	1	0	1
6=Post laser/cryo (do not use stages)	0	2	11	38	1	0	108	7	167
9=Old scars, but no active ROP	0	0	0	7	24	3	3	0	37
Total	6	37	395	4335	1245	622	114	22	6776

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Highest stage in lowest zone vs. highest stage in any zone

The FREQ Procedure

Table of SP10LHLZ by SP10LHAZ

SP10LHLZ(Left-Highest stage in lowest zone)	SP10LHAZ(Left-Highest stage in any zone)										
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	4=Stage 4a or 4b	5=Stage 5	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	6	0	0	0	0	0	0	0	0	0	6
P=Permanently missing	0	53	0	0	0	0	0	0	4	0	57
0=No ROP	0	0	3172	3	2	0	0	0	0	0	3177
1=Stage 1	0	1	6	1410	5	2	0	0	0	0	1424
2=Stage 2	0	0	13	9	1407	15	0	0	0	0	1444
3=Stage 3	0	0	0	1	0	487	0	0	0	0	488
4=Stage 4a or 4b	0	0	0	0	0	0	3	0	0	0	3
5=Stage 5	0	0	0	0	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	0	0	0	0	0	0	0	148	0	148
9=Old scars, but no active ROP	0	0	0	0	0	0	0	0	0	28	28
Total	6	54	3191	1423	1414	504	3	1	152	28	6776

Table of SP10RHLZ by SP10RHAZ

SP10RHLZ(Right-Highest stage in lowest zone)	SP10RHAZ(Right-Highest stage in any zone)										
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	4=Stage 4a or 4b	5=Stage 5	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	6	0	0	0	0	0	0	0	0	0	6
P=Permanently missing	0	50	0	0	0	0	0	0	4	0	54
0=No ROP	0	0	3208	4	2	0	0	0	0	0	3214
1=Stage 1	0	0	12	1359	7	2	0	0	0	0	1380
2=Stage 2	0	0	17	10	1410	12	0	0	0	0	1449
3=Stage 3	0	0	2	1	1	460	0	0	0	0	464
4=Stage 4a or 4b	0	1	3	0	0	0	3	0	0	0	7
5=Stage 5	0	0	0	0	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	0	1	0	0	0	0	0	163	0	164
9=Old scars, but no active ROP	0	0	0	0	0	0	0	0	0	37	37
Total	6	51	3243	1374	1420	474	3	1	167	37	6776

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The FREQ Procedure

Table of SP10LLWZ by SP10LTHR					
SP10LLWZ(Left-lowest zone of any vessels)	SP10LTHR(Left-Threshold (New Type 1))				
Frequency		*	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	12	23	4	39
1=I	0	0	346	20	366
2=II	0	6	4257	104	4367
3=III	0	1	1250	1	1252
4=Mature	0	4	622	0	626
5=Status post laser/cryo	0	6	89	6	101
9=Unable to determine	0	1	18	0	19
Total	6	30	6605	135	6776

Table of SP10LHLZ by SP10LTHR					
SP10LHLZ(Left-Highest stage in lowest zone)	SP10LTHR(Left-Threshold (New Type 1))				
Frequency		*	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	17	37	3	57
0=No ROP	0	1	3176	0	3177
1=Stage 1	0	0	1422	2	1424
2=Stage 2	0	3	1415	26	1444
3=Stage 3	0	2	390	96	488
4=Stage 4a or 4b	0	0	3	0	3
5=Stage 5	0	0	0	1	1
6=Post laser/cryo (do not use stages)	0	7	134	7	148
9=Old scars, but no active ROP	0	0	28	0	28
Total	6	30	6605	135	6776

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The FREQ Procedure

Table of SP10LHAZ by SP10LTHR					
SP10LHAZ(Left-Highest stage in any zone)	SP10LTHR(Left-Threshold (New Type 1))				
Frequency		*	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	16	35	3	54
0=No ROP	0	1	3190	0	3191
1=Stage 1	0	0	1421	2	1423
2=Stage 2	0	2	1389	23	1414
3=Stage 3	0	3	402	99	504
4=Stage 4a or 4b	0	0	3	0	3
5=Stage 5	0	0	0	1	1
6=Post laser/cryo (do not use stages)	0	8	137	7	152
9=Old scars, but no active ROP	0	0	28	0	28
Total	6	30	6605	135	6776

Table of SP10LDET by SP10LTHR					
SP10LDET(Left-Post surgical Retinal Detachment)	SP10LTHR(Left-Threshold (New Type 1))				
Frequency		*	N	Y	Total
.	6	0	456	4	466
P=Permanently missing	0	12	12	1	25
0=None	0	18	6134	129	6281
3=Partial, not involving macula (stage 4a)	0	0	1	0	1
4=Partial, does involve macula (stage 4b)	0	0	1	1	2
9=View obscured, can't tell	0	0	1	0	1
Total	6	30	6605	135	6776

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SUPP10 Cross-tabulations (All exams)
Threshold (new Type 1) ROP vs. other variables

The FREQ Procedure

Table of SP10RLWZ by SP10RTHR					
SP10RLWZ(Right-lowest zone of any vessels)	SP10RTHR(Right-Threshold (New Type 1))				
Frequency	.	*	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	10	23	4	37
1=I	0	1	364	30	395
2=II	0	5	4234	96	4335
3=III	0	0	1245	0	1245
4=Mature	0	3	619	0	622
5=Status post laser/cryo	0	7	102	5	114
9=Unable to determine	0	2	20	0	22
Total	6	28	6607	135	6776

Table of SP10RHLZ by SP10RTHR					
SP10RHLZ(Right-Highest stage in lowest zone)	SP10RTHR(Right-Threshold (New Type 1))				
Frequency	.	*	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	15	36	3	54
0=No ROP	0	1	3213	0	3214
1=Stage 1	0	0	1377	3	1380
2=Stage 2	0	2	1421	26	1449
3=Stage 3	0	1	370	93	464
4=Stage 4a or 4b	0	1	6	0	7
5=Stage 5	0	0	0	1	1
6=Post laser/cryo (do not use stages)	0	8	147	9	164
9=Old scars, but no active ROP	0	0	37	0	37
Total	6	28	6607	135	6776

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The FREQ Procedure

Table of SP10RHAZ by SP10RTHR					
SP10RHAZ(Right-Highest stage in any zone)	SP10RTHR(Right-Threshold (New Type 1))				
Frequency		.	N	Y	Total
.	6	0	0	0	6
P=Permanently missing	0	15	33	3	51
0=No ROP	0	1	3242	0	3243
1=Stage 1	0	0	1371	3	1374
2=Stage 2	0	1	1395	24	1420
3=Stage 3	0	2	377	95	474
4=Stage 4a or 4b	0	0	3	0	3
5=Stage 5	0	0	0	1	1
6=Post laser/cryo (do not use stages)	0	9	149	9	167
9=Old scars, but no active ROP	0	0	37	0	37
Total	6	28	6607	135	6776

Table of SP10RDET by SP10RTHR					
SP10RDET(Right-Post surgical Retinal Detachment)	SP10RTHR(Right-Threshold (New Type 1))				
Frequency		.	N	Y	Total
.	6	0	458	3	467
P=Permanently missing	0	12	13	1	26
0=None	0	16	6134	129	6279
3=Partial, not involving macula (stage 4a)	0	0	2	0	2
4=Partial, does involve macula (stage 4b)	0	0	0	1	1
5=Complete	0	0	0	1	1
Total	6	28	6607	135	6776

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SUPP10 Cross-tabulations (All exams)
Surgery vs. other variables

The FREQ Procedure

Table of SP10LLWZ by SP10LSRG

SP10LLWZ(Left-lowest zone of any vessels)	SP10LSRG(Left-Surgery)								
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	4=Scleral buckle	5=Vitrectomy	6=Other	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	5	28	5	0	0	1	0	39
1=I	0	3	343	20	0	0	0	0	366
2=II	0	10	4275	77	2	0	0	3	4367
3=III	0	2	1248	1	1	0	0	0	1252
4=Mature	0	5	620	0	0	1	0	0	626
5=Status post laser/cryo	0	0	89	11	0	0	0	1	101
9=Unable to determine	0	1	18	0	0	0	0	0	19
Total	6	26	6621	114	3	1	1	4	6776

Table of SP10LHLZ by SP10LSRG

SP10LHLZ(Left-Highest stage in lowest zone)	SP10LSRG(Left-Surgery)								
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	4=Scleral buckle	5=Vitrectomy	6=Other	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	11	42	4	0	0	0	0	57
0=No ROP	0	9	3167	0	0	1	0	0	3177
1=Stage 1	0	3	1421	0	0	0	0	0	1424
2=Stage 2	0	0	1428	14	1	0	0	1	1444
3=Stage 3	0	1	400	84	1	0	0	2	488
4=Stage 4a or 4b	0	0	3	0	0	0	0	0	3
5=Stage 5	0	0	0	1	0	0	0	0	1
6=Post laser/cryo (do not use stages)	0	2	133	11	0	0	1	1	148
9=Old scars, but no active ROP	0	0	27	0	1	0	0	0	28
Total	6	26	6621	114	3	1	1	4	6776

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The FREQ Procedure

Table of SP10LHAZ by SP10LSRG									
SP10LHAZ(Left-Highest stage in any zone)	SP10LSRG(Left-Surgery)								
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	4=Scleral buckle	5=Vitrectomy	6=Other	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	12	38	4	0	0	0	0	54
0=No ROP	0	9	3181	0	0	1	0	0	3191
1=Stage 1	0	2	1421	0	0	0	0	0	1423
2=Stage 2	0	0	1401	11	1	0	0	1	1414
3=Stage 3	0	1	413	87	1	0	0	2	504
4=Stage 4a or 4b	0	0	3	0	0	0	0	0	3
5=Stage 5	0	0	0	1	0	0	0	0	1
6=Post laser/cryo (do not use stages)	0	2	137	11	0	0	1	1	152
9=Old scars, but no active ROP	0	0	27	0	1	0	0	0	28
Total	6	26	6621	114	3	1	1	4	6776

Table of SP10LTHR by SP10LSRG									
SP10LTHR(Left-Threshold (New Type 1))	SP10LSRG(Left-Surgery)								
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	4=Scleral buckle	5=Vitrectomy	6=Other	Total
	6	0	0	0	0	0	0	0	6
*	0	11	15	3	0	0	1	0	30
N	0	15	6535	50	2	1	0	2	6605
Y	0	0	71	61	1	0	0	2	135
Total	6	26	6621	114	3	1	1	4	6776

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The FREQ Procedure

Table of SP10LDET by SP10LSRG

SP10LDET(Left-Post surgical Retinal Detachment)	SP10LSRG(Left-Surgery)								
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	4=Scleral buckle	5=Vitrectomy	6=Other	Total
.	6	3	457	0	0	0	0	0	466
P=Permanently missing	0	21	2	2	0	0	0	0	25
0=None	0	2	6160	111	2	1	1	4	6281
3=Partial, not involving macula (stage 4a)	0	0	1	0	0	0	0	0	1
4=Partial, does involve macula (stage 4b)	0	0	1	1	0	0	0	0	2
9=View obscured, can't tell	0	0	0	0	1	0	0	0	1
Total	6	26	6621	114	3	1	1	4	6776

Table of SP10RLWZ by SP10RSRG

SP10RLWZ(Right-lowest zone of any vessels)	SP10RSRG(Right-Surgery)						
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
.	6	0	0	0	0	0	6
P=Permanently missing	0	6	25	6	0	0	37
1=I	0	3	368	24	0	0	395
2=II	0	11	4240	79	2	3	4335
3=III	0	1	1243	1	0	0	1245
4=Mature	0	4	618	0	0	0	622
5=Status post laser/cryo	0	0	103	11	0	0	114
9=Unable to determine	0	2	20	0	0	0	22
Total	6	27	6617	121	2	3	6776

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SUPP10 Cross-tabulations (All exams) Surgery vs. other variables

The FREQ Procedure

Table of SP10RHLZ by SP10RSRG							
SP10RHLZ(Right-Highest stage in lowest zone)	SP10RSRG(Right-Surgery)						
Frequency		P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
	6	0	0	0	0	0	6
P=Permanently missing	0	11	38	5	0	0	54
0=No ROP	0	9	3205	0	0	0	3214
1=Stage 1	0	3	1377	0	0	0	1380
2=Stage 2	0	0	1430	17	1	1	1449
3=Stage 3	0	1	375	85	1	2	464
4=Stage 4a or 4b	0	1	6	0	0	0	7
5=Stage 5	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	2	149	13	0	0	164
9=Old scars, but no active ROP	0	0	37	0	0	0	37
Total	6	27	6617	121	2	3	6776

Table of SP10RHAZ by SP10RSRG							
SP10RHAZ(Right-Highest stage in any zone)	SP10RSRG(Right-Surgery)						
Frequency		P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
	6	0	0	0	0	0	6
P=Permanently missing	0	12	34	5	0	0	51
0=No ROP	0	9	3234	0	0	0	3243
1=Stage 1	0	3	1371	0	0	0	1374
2=Stage 2	0	0	1403	15	1	1	1420
3=Stage 3	0	1	383	87	1	2	474
4=Stage 4a or 4b	0	0	3	0	0	0	3
5=Stage 5	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	2	152	13	0	0	167
9=Old scars, but no active ROP	0	0	37	0	0	0	37
Total	6	27	6617	121	2	3	6776

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SUPP10 Cross-tabulations (All exams)
Surgery vs. other variables

The FREQ Procedure

Table of SP10RTHR by SP10RSRG							
SP10RTHR(Right-Threshold (New Type 1))	SP10RSRG(Right-Surgery)						
Frequency		P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
	6	0	0	0	0	0	6
*	0	11	12	5	0	0	28
N	0	16	6537	53	1	0	6607
Y	0	0	68	63	1	3	135
Total	6	27	6617	121	2	3	6776

Table of SP10RDET by SP10RSRG							
SP10RDET(Right-Post surgical Retinal Detachment)	SP10RSRG(Right-Surgery)						
Frequency		P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
	6	3	458	0	0	0	467
P=Permanently missing	0	22	2	2	0	0	26
0=None	0	2	6155	117	2	3	6279
3=Partial, not involving macula (stage 4a)	0	0	2	0	0	0	2
4=Partial, does involve macula (stage 4b)	0	0	0	1	0	0	1
5=Complete	0	0	0	1	0	0	1
Total	6	27	6617	121	2	3	6776

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SUPP10 Cross-tabulations (All exams)
Comparison of left vs. right eye

The FREQ Procedure

Table of SP10LLWZ by SP10RLWZ

SP10LLWZ(Left-lowest zone of any vessels)	SP10RLWZ(Right-lowest zone of any vessels)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	6	0	0	0	0	0	0	0	6
P=Permanently missing	0	32	1	6	0	0	0	0	39
1=I	0	0	357	9	0	0	0	0	366
2=II	0	3	36	4276	38	2	11	1	4367
3=III	0	1	1	39	1187	22	1	1	1252
4=Mature	0	1	0	5	20	598	1	1	626
5=Status post laser/cryo	0	0	0	0	0	0	101	0	101
9=Unable to determine	0	0	0	0	0	0	0	19	19
Total	6	37	395	4335	1245	622	114	22	6776

Table of SP10LHLZ by SP10RHLZ

SP10LHLZ(Left-Highest stage in lowest zone)	SP10RHLZ(Right-Highest stage in lowest zone)										
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	4=Stage 4a or 4b	5=Stage 5	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	6	0	0	0	0	0	0	0	0	0	6
P=Permanently missing	0	49	2	3	2	0	1	0	0	0	57
0=No ROP	0	1	3060	84	20	5	3	0	2	2	3177
1=Stage 1	0	1	119	1210	80	12	0	0	1	1	1424
2=Stage 2	0	1	25	73	1263	68	0	0	7	7	1444
3=Stage 3	0	2	7	10	84	379	0	0	6	0	488
4=Stage 4a or 4b	0	0	0	0	0	0	3	0	0	0	3
5=Stage 5	0	0	0	0	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	0	0	0	0	0	0	0	148	0	148
9=Old scars, but no active ROP	0	0	1	0	0	0	0	0	0	27	28
Total	6	54	3214	1380	1449	464	7	1	164	37	6776

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SUPP10 Cross-tabulations (All exams)
Comparison of left vs. right eye

The FREQ Procedure

Table of SP10LHAZ by SP10RHAZ

SP10LHAZ(Left-Highest stage in any zone)	SP10RHAZ(Right-Highest stage in any zone)										
Frequency		P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	4=Stage 4a or 4b	5=Stage 5	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	6	0	0	0	0	0	0	0	0	0	6
P=Permanently missing	0	46	2	4	2	0	0	0	0	0	54
0=No ROP	0	2	3086	83	13	3	0	0	2	2	3191
1=Stage 1	0	1	122	1206	79	13	0	0	1	1	1423
2=Stage 2	0	0	24	70	1238	68	0	0	7	7	1414
3=Stage 3	0	2	7	11	88	390	0	0	6	0	504
4=Stage 4a or 4b	0	0	0	0	0	0	3	0	0	0	3
5=Stage 5	0	0	0	0	0	0	0	1	0	0	1
6=Post laser/cryo (do not use stages)	0	0	1	0	0	0	0	0	151	0	152
9=Old scars, but no active ROP	0	0	1	0	0	0	0	0	0	27	28
Total	6	51	3243	1374	1420	474	3	1	167	37	6776

Table of SP10LTHR by SP10RTHR

SP10LTHR(Left-Threshold (New Type 1))	SP10RTHR(Right-Threshold (New Type 1))				
Frequency		*	N	Y	Total
	6	0	0	0	6
*	0	24	6	0	30
N	0	3	6585	17	6605
Y	0	1	16	118	135
Total	6	28	6607	135	6776

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SUPP10 Cross-tabulations (All exams)
Comparison of left vs. right eye

The FREQ Procedure

Table of SP10LSRG by SP10RSRG							
SP10LSRG(Left-Surgery)	SP10RSRG(Right-Surgery)						
Frequency	.	P=Permanently missing	0=No surgery this day	1=Laser	3=Both laser/cryo	6=Other	Total
.	6	0	0	0	0	0	6
P=Permanently missing	0	24	2	0	0	0	26
0=No surgery this day	0	3	6608	10	0	0	6621
1=Laser	0	0	4	110	0	0	114
3=Both laser/cryo	0	0	1	0	2	0	3
4=Scleral buckle	0	0	1	0	0	0	1
5=Vitrectomy	0	0	0	1	0	0	1
6=Other	0	0	1	0	0	3	4
Total	6	27	6617	121	2	3	6776

Table of SP10LDET by SP10RDET							
SP10LDET(Left-Post surgical Retinal Detachment)	SP10RDET(Right-Post surgical Retinal Detachment)						
Frequency	.	P=Permanently missing	0=None	3=Partial, not involving macula (stage 4a)	4=Partial, does involve macula (stage 4b)	5=Complete	Total
.	462	0	4	0	0	0	466
P=Permanently missing	0	23	2	0	0	0	25
0=None	5	3	6272	0	0	1	6281
3=Partial, not involving macula (stage 4a)	0	0	0	1	0	0	1
4=Partial, does involve macula (stage 4b)	0	0	0	1	1	0	2
9=View obscured, can't tell	0	0	1	0	0	0	1
Total	467	26	6279	2	1	1	6776

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Lowest zone for current exam vs. previous exam

The FREQ Procedure

Table of SP10LLWZ by prevlzone									
SP10LLWZ(Left-lowest zone of any vessels)	prevlzone(Left lowest zone of any vessels - previous exam)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	1	0	0	4	1	0	0	0	6
P=Permanently missing	14	10	2	13	0	0	0	0	39
1=I	167	3	159	37	0	0	0	0	366
2=II	837	18	175	3283	50	2	0	2	4367
3=III	78	6	4	599	564	0	0	1	1252
4=Mature	6	3	3	255	325	33	0	1	626
5=Status post laser/cryo	0	2	4	29	0	0	66	0	101
9=Unable to determine	2	0	0	4	1	0	0	12	19
Total	1105	42	347	4224	941	35	66	16	6776

Table of SP10RLWZ by prevrzone									
SP10RLWZ(Right-lowest zone of any vessels)	prevrzone(Right lowest zone of any vessels - previous exam)								
Frequency	.	P=Permanently missing	1=I	2=II	3=III	4=Mature	5=Status post laser/cryo	9=Unable to determine	Total
.	1	0	0	4	1	0	0	0	6
P=Permanently missing	11	10	2	13	0	1	0	0	37
1=I	174	4	181	36	0	0	0	0	395
2=II	829	16	176	3257	52	2	0	3	4335
3=III	82	4	4	594	558	2	0	1	1245
4=Mature	6	3	5	251	326	29	0	2	622
5=Status post laser/cryo	0	2	5	30	0	0	77	0	114
9=Unable to determine	2	0	0	5	3	0	0	12	22
Total	1105	39	373	4190	940	34	77	18	6776

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SUPP10 Cross-tabulations (All exams)
Highest stage (in lowest any zone) for current exam vs. previous exam

The FREQ Procedure

Table of SP10LHLZ by previstage									
SP10LHLZ(Left-Highest stage in lowest zone)	previstage(Left highest stage in lowest zone - previous exam)								
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	1	0	4	0	1	0	0	0	6
P=Permanently missing	11	18	6	7	7	7	1	0	57
0=No ROP	906	12	1798	320	112	22	1	6	3177
1=Stage 1	132	4	361	739	180	8	0	0	1424
2=Stage 2	53	10	138	247	926	68	0	2	1444
3=Stage 3	1	1	28	29	145	284	0	0	488
4=Stage 4a or 4b	0	0	0	2	1	0	0	0	3
5=Stage 5	0	0	0	0	1	0	0	0	1
6=Post laser/cryo (do not use stages)	0	3	0	0	14	29	102	0	148
9=Old scars, but no active ROP	1	2	2	4	5	1	1	12	28
Total	1105	50	2337	1348	1392	419	105	20	6776

Table of SP10LHAZ by previstany									
SP10LHAZ(Left-Highest stage in any zone)	previstany(Left highest stage in any zone - previous exam)								
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	1	0	4	0	1	0	0	0	6
P=Permanently missing	11	15	6	8	6	7	1	0	54
0=No ROP	913	12	1806	322	110	21	1	6	3191
1=Stage 1	133	4	366	736	177	7	0	0	1423
2=Stage 2	45	11	140	243	905	68	0	2	1414
3=Stage 3	1	1	29	30	146	297	0	0	504
4=Stage 4a or 4b	0	0	0	2	1	0	0	0	3
5=Stage 5	0	0	0	0	1	0	0	0	1
6=Post laser/cryo (do not use stages)	0	3	0	0	12	32	105	0	152
9=Old scars, but no active ROP	1	2	2	4	5	1	1	12	28
Total	1105	48	2353	1345	1364	433	108	20	6776

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SUPP10 Cross-tabulations (All exams)
Highest stage (in lowest/any zone) for current exam vs. previous exam

The FREQ Procedure

Table of SP10RHLZ by prevrstage

SP10RHLZ(Right-Highest stage in lowest zone)	prevrstage(Right highest stage in lowest zone - previous exam)								
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	1	0	4	0	1	0	0	0	6
P=Permanently missing	9	16	8	7	6	7	1	0	54
0=No ROP	901	11	1850	318	106	22	1	5	3214
1=Stage 1	132	4	343	723	167	11	0	0	1380
2=Stage 2	59	9	143	222	953	62	0	1	1449
3=Stage 3	2	2	28	30	140	261	0	1	464
4=Stage 4a or 4b	0	0	2	2	3	0	0	0	7
5=Stage 5	0	0	0	0	1	0	0	0	1
6=Post laser/cryo (do not use stages)	0	3	0	0	14	32	115	0	164
9=Old scars, but no active ROP	1	2	0	4	7	1	1	21	37
Total	1105	47	2378	1306	1398	396	118	28	6776

Table of SP10RHAZ by prevrstany

SP10RHAZ(RIght-Highest stage in any zone)	prevrstany(Right highest stage in any zone - previous exam)								
Frequency	.	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
.	1	0	4	0	1	0	0	0	6
P=Permanently missing	9	13	8	8	6	6	1	0	51
0=No ROP	910	12	1875	316	104	19	2	5	3243
1=Stage 1	135	3	340	718	165	13	0	0	1374
2=Stage 2	48	10	146	220	930	65	0	1	1420
3=Stage 3	1	1	30	31	143	267	0	1	474
4=Stage 4a or 4b	0	0	1	1	1	0	0	0	3
5=Stage 5	0	0	0	0	1	0	0	0	1
6=Post laser/cryo (do not use stages)	0	3	1	0	13	34	116	0	167
9=Old scars, but no active ROP	1	2	0	4	7	1	1	21	37
Total	1105	44	2405	1298	1371	405	120	28	6776

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Left eye - highest stage in lowest zone for current vs. previous exam where zone 3 for 2 consecutive visits

The FREQ Procedure

Table of SP10LHLZ by previstage

SP10LHLZ(Left-Highest stage in lowest zone)	previstage(Left highest stage in lowest zone - previous exam)							
Frequency	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	6=Post laser/cryo (do not use stages)	9=Old scars, but no active ROP	Total
P=Permanently missing	1	0	2	1	0	0	0	4
0=No ROP	1	214	47	20	4	0	0	286
1=Stage 1	0	17	135	31	0	0	0	183
2=Stage 2	1	5	7	46	1	0	0	60
3=Stage 3	0	2	1	5	10	0	0	18
4=Stage 4a or 4b	0	0	1	0	0	0	0	1
6=Post laser/cryo (do not use stages)	0	0	0	0	0	1	0	1
9=Old scars, but no active ROP	0	2	2	0	1	0	6	11
Total	3	240	195	103	16	1	6	564

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SUPP10 Cross-tabulations (All exams)

Right eye - highest stage in lowest zone for current vs. previous exam where zone 3 for 2 consecutive visits

The FREQ Procedure

Table of SP10RHLZ by prevrstage							
SP10RHLZ(Right-Highest stage in lowest zone)	prevrstage(Right highest stage in lowest zone - previous exam)						
Frequency	P=Permanently missing	0=No ROP	1=Stage 1	2=Stage 2	3=Stage 3	9=Old scars, but no active ROP	Total
P=Permanently missing	1	0	1	2	0	0	4
0=No ROP	1	228	49	17	4	0	299
1=Stage 1	0	18	108	29	1	0	156
2=Stage 2	1	4	3	51	3	0	62
3=Stage 3	0	1	1	7	11	0	20
4=Stage 4a or 4b	0	0	1	0	0	0	1
9=Old scars, but no active ROP	0	0	2	0	1	13	16
Total	3	251	165	106	20	13	558

Current and previous exam results for infants with left eye ROP Type 1 due to threshold (new type 1) ROP

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	40	21	P=Permanently missing	P=Permanently missing	P=Permanently missing	2=II	1=Stage 1	1=Stage 1
2	35	7	1=I	3=Stage 3	3=Stage 3	1=I	1=Stage 1	1=Stage 1
3	37	8	1=I	3=Stage 3	3=Stage 3	1=I	1=Stage 1	1=Stage 1
4	34	5	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
5	37	5	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
6	37	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
7	34	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
8	34	8	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
9	40	14	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
10	35	16	1=I	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
11	35	7	1=I	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
12	38	7	1=I	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
13	32	7	2=II	1=Stage 1	1=Stage 1	2=II	0=No ROP	0=No ROP
14	33	13	2=II	1=Stage 1	1=Stage 1	2=II	0=No ROP	0=No ROP
15	35	7	2=II	2=Stage 2	2=Stage 2	1=I	2=Stage 2	2=Stage 2
16	33	4	2=II	2=Stage 2	2=Stage 2	2=II	0=No ROP	0=No ROP
17	34	14	2=II	2=Stage 2	2=Stage 2	2=II	0=No ROP	0=No ROP
18	34	14	2=II	2=Stage 2	2=Stage 2	2=II	0=No ROP	0=No ROP
19	34	3	2=II	2=Stage 2	2=Stage 2	2=II	1=Stage 1	1=Stage 1
20	37	7	2=II	2=Stage 2	2=Stage 2	2=II	1=Stage 1	1=Stage 1
21	41	6	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
22	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
23	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
24	38	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
25	40	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
26	44	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
27	34	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
28	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
29	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
30	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
31	39	8	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
32	44	8	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
33	43	10	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
34	36	23	2=II	2=Stage 2	3=Stage 3	2=II	0=No ROP	0=No ROP
35	34	14	2=II	2=Stage 2	3=Stage 3	2=II	1=Stage 1	1=Stage 1
36	35	6	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=Y due to threshold (new type 1) ROP

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
37	35	7	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
38	35	7	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
39	34	8	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
40	34	21	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
41	36	1	2=II	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
42	35	14	2=II	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
43	33	5	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
44	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
45	34	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
46	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
47	38	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
48	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
49	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
50	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
51	39	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
52	39	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
53	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
54	37	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
55	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
56	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
57	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
58	35	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
59	36	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
60	36	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
61	39	14	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
62	40	14	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
63	36	1	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
64	37	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
65	34	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
66	36	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
67	36	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
68	37	3	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
69	35	3	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
70	38	4	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
71	40	4	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
72	38	5	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with left eye ROP=Y due to threshold (new type 1) ROP

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
73	34	6	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
74	41	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
75	36	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
76	40	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
77	36	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
78	40	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
79	38	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
80	40	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
81	38	8	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
82	40	10	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
83	41	15	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2

Current and previous exam results for infants with right eye ROP Y due to threshold (new type 1) ROP

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	40	21	P=Permanently missing	P=Permanently missing	P=Permanently missing	2=II	1=Stage 1	1=Stage 1
2	44	7	1=I	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
3	37	7	1=I	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
4	35	7	1=I	3=Stage 3	3=Stage 3	1=I	1=Stage 1	1=Stage 1
5	34	5	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
6	37	5	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
7	36	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
8	37	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
9	39	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
10	34	7	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
11	34	8	1=I	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
12	35	16	1=I	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
13	35	7	1=I	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
14	38	7	1=I	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
15	37	8	1=I	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
16	32	7	2=II	1=Stage 1	1=Stage 1	2=II	0=No ROP	0=No ROP
17	38	14	2=II	1=Stage 1	1=Stage 1	2=II	0=No ROP	0=No ROP
18	34	14	2=II	1=Stage 1	1=Stage 1	2=II	1=Stage 1	1=Stage 1
19	33	4	2=II	2=Stage 2	2=Stage 2	2=II	0=No ROP	0=No ROP
20	34	14	2=II	2=Stage 2	2=Stage 2	2=II	0=No ROP	0=No ROP
21	34	3	2=II	2=Stage 2	2=Stage 2	2=II	1=Stage 1	1=Stage 1
22	37	7	2=II	2=Stage 2	2=Stage 2	2=II	1=Stage 1	1=Stage 1
23	41	6	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
24	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
25	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
26	38	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
27	40	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
28	34	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
29	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
30	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
31	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
32	35	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
33	37	7	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
34	39	8	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
35	43	10	2=II	2=Stage 2	2=Stage 2	2=II	2=Stage 2	2=Stage 2
36	36	23	2=II	2=Stage 2	3=Stage 3	2=II	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=Y due to threshold (new type 1) ROP

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
37	35	7	2=II	3=Stage 3	3=Stage 3	1=I	2=Stage 2	2=Stage 2
38	35	6	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
39	35	7	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
40	35	7	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
41	34	8	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
42	34	21	2=II	3=Stage 3	3=Stage 3	2=II	0=No ROP	0=No ROP
43	35	14	2=II	3=Stage 3	3=Stage 3	2=II	1=Stage 1	1=Stage 1
44	36	1	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
45	33	5	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
46	34	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
47	34	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
48	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
49	38	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
50	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
51	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
52	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
53	39	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
54	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
55	37	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
56	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
57	40	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
58	36	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
59	35	7	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
60	35	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
61	36	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
62	36	8	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
63	39	14	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
64	40	14	2=II	3=Stage 3	3=Stage 3	2=II	2=Stage 2	2=Stage 2
65	38	1	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
66	36	1	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
67	35	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
68	37	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
69	37	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
70	34	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
71	36	2	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
72	37	3	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3

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Current and previous exam results for infants with right eye ROP - due to threshold (new type 1) ROP

Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
73	35	3	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
74	38	4	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
75	40	4	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
76	34	6	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
77	35	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
78	41	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
79	36	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
80	40	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
81	39	7	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3
82	38	8	2=II	3=Stage 3	3=Stage 3	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with left eye ROP=Y due to ROP surgery

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Surgery	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	34	1	P=Permanently missing	P=Permanently missing	1=Laser	1=I	3=Stage 3	3=Stage 3
2	36	1	P=Permanently missing	P=Permanently missing	1=Laser	2=II	2=Stage 2	2=Stage 2
3	34	7	1=I	2=Stage 2	1=Laser	1=I	2=Stage 2	2=Stage 2
4	35	4	1=I	3=Stage 3	1=Laser	1=I	2=Stage 2	2=Stage 2
5	33	7	1=I	3=Stage 3	1=Laser	1=I	2=Stage 2	2=Stage 2
6	37	0	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
7	32	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
8	37	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
9	34	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
10	38	2	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
11	36	1	1=I	6=Post laser/cryo (do not use stages)	1=Laser	1=I	2=Stage 2	2=Stage 2
12	37	2	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
13	33	6	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
14	34	7	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
15	37	7	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
16	44	7	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	3=Stage 3
17	37	1	2=II	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
18	53	17	2=II	3=Stage 3	1=Laser	2=II	0=No ROP	0=No ROP
19	35	2	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
20	36	3	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
21	35	4	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
22	36	7	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
23	44	10	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
24	34	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
25	32	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
26	35	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
27	38	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
28	35	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
29	40	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
30	37	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
31	37	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
32	40	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
33	38	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
34	36	2	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
35	40	2	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with left eye ROP=Y due to ROP surgery

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Surgery	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
36	38	4	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
37	35	5	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
38	44	6	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
39	35	8	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
40	35	9	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
41	36	1	2=II	3=Stage 3	3=Both laser/cryo	2=II	2=Stage 2	2=Stage 2
42	37	33	3=III	9=Old scars, but no active ROP	3=Both laser/cryo	3=III	0=No ROP	0=No ROP
43	50	36	4=Mature	0=No ROP	4=Scleral buckle	3=III	1=Stage 1	1=Stage 1
44	39	13	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	0=No surgery this day	2=II	3=Stage 3	3=Stage 3
45	41	4	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	1=Laser	2=II	3=Stage 3	3=Stage 3
46	40	7	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	1=Laser	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with right eye ROP=Y due to ROP surgery

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Surgery	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	34	1	P=Permanently missing	P=Permanently missing	1=Laser	1=I	3=Stage 3	3=Stage 3
2	36	1	P=Permanently missing	P=Permanently missing	1=Laser	2=II	2=Stage 2	2=Stage 2
3	34	7	1=I	2=Stage 2	1=Laser	1=I	2=Stage 2	2=Stage 2
4	35	4	1=I	3=Stage 3	1=Laser	1=I	2=Stage 2	2=Stage 2
5	33	7	1=I	3=Stage 3	1=Laser	1=I	2=Stage 2	2=Stage 2
6	37	0	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
7	32	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
8	37	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
9	34	1	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
10	38	2	1=I	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
11	36	1	1=I	6=Post laser/cryo (do not use stages)	1=Laser	1=I	2=Stage 2	2=Stage 2
12	36	2	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
13	35	4	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
14	33	6	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
15	34	7	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	2=Stage 2
16	44	7	2=II	2=Stage 2	1=Laser	2=II	2=Stage 2	3=Stage 3
17	35	9	2=II	3=Stage 3	1=Laser	1=I	2=Stage 2	2=Stage 2
18	37	1	2=II	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
19	37	2	2=II	3=Stage 3	1=Laser	1=I	3=Stage 3	3=Stage 3
20	53	17	2=II	3=Stage 3	1=Laser	2=II	0=No ROP	0=No ROP
21	40	1	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
22	35	2	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
23	36	7	2=II	3=Stage 3	1=Laser	2=II	2=Stage 2	2=Stage 2
24	32	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
25	35	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
26	35	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
27	40	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
28	37	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
29	37	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
30	38	1	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
31	36	2	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
32	40	2	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
33	40	2	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
34	36	3	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
35	35	3	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with right eye ROP=Y due to ROP surgery

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Surgery	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
36	38	4	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
37	35	5	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
38	44	6	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
39	40	7	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
40	35	8	2=II	3=Stage 3	1=Laser	2=II	3=Stage 3	3=Stage 3
41	36	1	2=II	3=Stage 3	3=Both laser/cryo	2=II	3=Stage 3	3=Stage 3
42	41	15	3=III	3=Stage 3	1=Laser	3=III	2=Stage 2	2=Stage 2
43	36	11	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	0=No surgery this day	2=II	2=Stage 2	2=Stage 2
44	39	13	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	0=No surgery this day	2=II	3=Stage 3	3=Stage 3
45	41	4	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	1=Laser	2=II	3=Stage 3	3=Stage 3

Current and previous exam results for infants with left eye ROP=Y due to ROP stage 4-5

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	46	16	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	2=II	2=Stage 2	2=Stage 2
2	53	19	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1
3	49	21	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with right eye ROP = 1 due to ROP stage 4-5

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	40	14	2=II	4=Stage 4a or 4b	P=Permanently missing	2=II	1=Stage 1	1=Stage 1
2	39	29	2=II	4=Stage 4a or 4b	0=No ROP	2=II	0=No ROP	0=No ROP
3	39	22	2=II	4=Stage 4a or 4b	0=No ROP	2=II	2=Stage 2	2=Stage 2
4	52	29	2=II	4=Stage 4a or 4b	0=No ROP	2=II	2=Stage 2	2=Stage 2
5	46	16	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	2=II	2=Stage 2	2=Stage 2
6	53	19	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1
7	49	21	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=Y due to Avastin (surgery field F5ed)

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Surgery	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	40	8	2=II	2=Stage 2	2=Stage 2	6=Other	2=II	2=Stage 2	2=Stage 2

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Current and previous exam results for infants with right eye ROP=Y due to Avastin (surgery field F5ed)

Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Surgery	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	40	8	2=II	2=Stage 2	2=Stage 2	6=Other	2=II	2=Stage 2	2=Stage 2

Current and previous exam results for infants with left eye ROP=Y due to ROP stage 4-5

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	46	16	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	2=II	2=Stage 2	2=Stage 2
2	53	19	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1
3	49	21	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1

Thursday, August 27, 2009
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Current and previous exam results for infants with right eye ROP=Y due to ROP stage 4-5

Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	40	14	2=II	4=Stage 4a or 4b	P=Permanently missing	2=II	1=Stage 1	1=Stage 1
2	39	29	2=II	4=Stage 4a or 4b	0=No ROP	2=II	0=No ROP	0=No ROP
3	39	22	2=II	4=Stage 4a or 4b	0=No ROP	2=II	2=Stage 2	2=Stage 2
4	52	29	2=II	4=Stage 4a or 4b	0=No ROP	2=II	2=Stage 2	2=Stage 2
5	46	16	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	2=II	2=Stage 2	2=Stage 2
6	53	19	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	1=Stage 1	1=Stage 1
7	49	21	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=N due to Lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
1	38	7	3=III	P=Permanently missing	P=Permanently missing	3=III	1=Stage 1	1=Stage 1
2	41	13	3=III	P=Permanently missing	P=Permanently missing	3=III	1=Stage 1	1=Stage 1
3	38	14	3=III	P=Permanently missing	P=Permanently missing	3=III	2=Stage 2	2=Stage 2
4	67	159	3=III	0=No ROP	0=No ROP	3=III	P=Permanently missing	P=Permanently missing
5	40	3	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
6	34	4	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
7	42	6	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
8	52	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
9	36	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
10	34	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
11	31	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
12	41	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
13	40	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
14	37	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
15	42	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
16	38	8	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
17	41	9	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
18	41	10	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
19	38	11	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
20	36	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
21	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
22	37	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
23	41	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
24	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
25	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
26	37	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
27	38	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
28	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
29	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
30	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
31	34	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
32	33	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
33	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
34	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=N due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
35	42	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
36	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
37	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
38	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
39	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
40	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
41	33	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
42	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
43	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
44	41	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
45	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
46	38	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
47	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
48	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
49	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
50	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
51	41	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
52	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
53	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
54	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
55	42	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
56	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
57	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
58	43	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
59	46	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
60	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
61	34	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
62	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
63	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
64	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
65	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
66	37	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
67	34	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
68	34	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
69	33	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
70	39	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left-eye ROP N due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
71	41	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
72	44	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
73	39	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
74	34	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
75	37	16	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
76	43	17	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
77	44	18	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
78	41	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
79	38	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
80	39	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
81	39	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
82	43	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
83	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
84	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
85	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
86	39	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
87	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
88	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
89	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
90	36	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
91	36	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
92	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
93	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
94	35	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
95	35	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
96	39	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
97	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
98	42	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
99	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
100	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
101	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
102	39	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
103	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
104	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
105	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
106	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=N due to lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
107	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
108	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
109	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
110	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
111	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
112	38	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
113	39	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
114	42	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
115	39	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
116	35	23	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
117	36	24	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
118	40	24	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
119	45	25	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
120	38	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
121	41	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
122	37	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
123	41	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
124	37	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
125	40	27	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
126	44	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
127	48	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
128	35	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
129	40	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
130	43	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
131	36	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
132	43	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
133	45	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
134	36	30	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
135	39	31	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
136	40	32	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
137	38	32	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
138	43	33	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
139	39	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
140	41	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
141	41	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
142	40	35	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with left eye ROP=N due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
143	43	36	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
144	43	36	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
145	40	37	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
146	42	41	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
147	45	42	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
148	44	42	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
149	37	44	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
150	44	48	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
151	56	56	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
152	39	57	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
153	49	67	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
154	47	69	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
155	46	70	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
156	64	92	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
157	59	164	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
158	56	172	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
159	74	181	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
160	63	189	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
161	70	198	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
162	76	282	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
163	51	33	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	1=Stage 1
164	45	6	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
165	39	8	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
166	40	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
167	39	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
168	38	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
169	37	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
170	38	15	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
171	40	18	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
172	40	18	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
173	38	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
174	46	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
175	37	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
176	43	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
177	38	21	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
178	38	21	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with left eye ROP=N due to Lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
179	37	22	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
180	42	27	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
181	41	28	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
182	38	28	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
183	44	28	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
184	57	134	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
185	70	184	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
186	40	8	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
187	42	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
188	41	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
189	38	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
190	40	15	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
191	39	19	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
192	47	21	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
193	48	21	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
194	46	36	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
195	50	43	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
196	52	66	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
197	53	106	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
198	34	7	3=III	0=No ROP	0=No ROP	3=III	3=Stage 3	3=Stage 3
199	53	35	3=III	0=No ROP	0=No ROP	3=III	3=Stage 3	3=Stage 3
200	34	7	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
201	35	13	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
202	36	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
203	34	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
204	43	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
205	34	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
206	36	15	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
207	37	18	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
208	37	21	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
209	37	21	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
210	36	28	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
211	42	28	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
212	43	35	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
213	44	0	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
214	39	3	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with left eye ROP=N due to Lowest zone = II for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
215	43	5	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
216	42	5	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
217	37	6	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
218	41	6	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
219	40	6	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
220	41	6	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
221	39	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
222	35	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
223	41	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
224	43	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
225	50	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
226	41	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
227	48	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
228	47	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
229	37	8	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
230	36	8	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
231	37	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
232	40	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
233	36	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
234	33	12	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
235	39	12	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
236	36	13	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
237	40	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
238	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
239	39	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
240	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
241	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
242	39	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
243	37	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
244	37	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
245	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
246	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
247	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
248	37	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
249	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
250	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with left eye ROP=N due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
251	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
252	35	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
253	44	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
254	42	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
255	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
256	47	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
257	35	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
258	51	15	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
259	37	16	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
260	42	16	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
261	45	17	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
262	39	18	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
263	42	18	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
264	39	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
265	42	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
266	43	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
267	42	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
268	43	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
269	41	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
270	53	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
271	42	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
272	46	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
273	40	22	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
274	41	22	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
275	46	25	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
276	39	27	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
277	52	28	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
278	38	29	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
279	48	34	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
280	39	39	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
281	48	55	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
282	92	163	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
283	70	182	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
284	41	16	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	0=No ROP
285	34	4	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
286	42	9	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2

Current and previous exam results for infants with left-eye ROP N due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
287	36	11	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
288	40	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
289	48	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
290	45	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
291	47	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
292	37	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
293	37	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
294	40	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
295	41	15	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
296	41	15	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
297	42	15	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
298	43	33	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
299	55	56	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
300	48	69	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
301	34	21	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
302	36	21	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
303	44	28	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
304	42	28	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
305	36	17	3=III	2=Stage 2	2=Stage 2	3=III	1=Stage 1	1=Stage 1
306	42	17	3=III	2=Stage 2	2=Stage 2	3=III	1=Stage 1	1=Stage 1
307	39	28	3=III	2=Stage 2	2=Stage 2	3=III	1=Stage 1	1=Stage 1
308	42	6	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
309	48	6	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
310	42	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
311	39	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
312	42	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
313	41	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
314	45	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
315	37	8	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
316	40	8	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
317	37	9	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
318	41	10	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
319	42	11	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
320	40	13	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
321	38	13	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
322	45	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2

Current and previous exam results for infants with left eye ROP=N due to Lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left lowest zone of any vessels - previous exam	Left highest stage in lowest zone - previous exam	Left highest stage in any zone - previous exam
323	43	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
324	40	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
325	40	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
326	42	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
327	43	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
328	42	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
329	43	16	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
330	39	21	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
331	54	21	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
332	45	23	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
333	35	17	3=III	2=Stage 2	3=Stage 3	3=III	1=Stage 1	1=Stage 1
334	42	14	3=III	3=Stage 3	3=Stage 3	3=III	0=No ROP	0=No ROP
335	46	49	3=III	3=Stage 3	3=Stage 3	3=III	1=Stage 1	1=Stage 1
336	41	7	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
337	38	14	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
338	41	18	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
339	38	2	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
340	39	7	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
341	39	14	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
342	44	18	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
343	53	35	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
344	43	7	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	1=Stage 1	1=Stage 1
345	54	28	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	1=Stage 1	1=Stage 1
346	41	9	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
347	42	13	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
348	50	35	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP

Current and previous exam results for infants with right eye ROP = 1 due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
1	41	13	3=III	P=Permanently missing	P=Permanently missing	3=III	1=Stage 1	1=Stage 1
2	38	7	3=III	P=Permanently missing	P=Permanently missing	3=III	2=Stage 2	2=Stage 2
3	38	14	3=III	P=Permanently missing	P=Permanently missing	3=III	2=Stage 2	2=Stage 2
4	67	159	3=III	0=No ROP	0=No ROP	3=III	P=Permanently missing	P=Permanently missing
5	40	3	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
6	34	4	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
7	42	6	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
8	52	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
9	34	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
10	36	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
11	31	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
12	50	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
13	41	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
14	40	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
15	37	7	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
16	38	8	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
17	41	10	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
18	38	11	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
19	40	12	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
20	36	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
21	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
22	37	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
23	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
24	38	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
25	37	13	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
26	38	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
27	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
28	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
29	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
30	34	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
31	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
32	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
33	34	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
34	33	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=No but with Lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
35	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
36	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
37	42	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
38	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
39	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
40	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
41	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
42	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
43	33	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
44	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
45	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
46	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
47	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
48	38	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
49	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
50	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
51	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
52	37	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
53	41	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
54	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
55	36	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
56	39	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
57	42	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
58	35	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
59	44	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
60	40	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
61	43	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
62	46	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
63	34	14	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
64	41	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
65	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
66	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
67	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
68	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
69	38	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
70	37	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=N due to Lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
71	34	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
72	34	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
73	33	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
74	39	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
75	41	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
76	36	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
77	44	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
78	39	15	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
79	37	16	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
80	43	17	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
81	44	18	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
82	39	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
83	41	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
84	38	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
85	39	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
86	39	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
87	43	19	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
88	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
89	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
90	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
91	39	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
92	35	20	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
93	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
94	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
95	36	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
96	36	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
97	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
98	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
99	35	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
100	35	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
101	39	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
102	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
103	42	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
104	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
105	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
106	38	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=1 due to lowest zone III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
107	39	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
108	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
109	40	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
110	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
111	37	21	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
112	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
113	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
114	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
115	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
116	37	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
117	38	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
118	39	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
119	42	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
120	39	22	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
121	35	23	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
122	36	24	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
123	40	24	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
124	45	25	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
125	38	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
126	41	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
127	37	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
128	41	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
129	37	26	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
130	40	27	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
131	42	27	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
132	44	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
133	41	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
134	48	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
135	42	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
136	35	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
137	40	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
138	43	28	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
139	36	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
140	43	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
141	45	29	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
142	36	30	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=No due to lowest zone III for consecutive exams

This document provides data for infants with right eye ROP=No due to lowest zone III for consecutive exams. Questions about information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
143	39	31	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
144	40	32	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
145	38	32	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
146	43	33	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
147	39	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
148	41	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
149	41	34	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
150	43	36	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
151	40	37	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
152	42	41	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
153	45	42	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
154	44	42	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
155	37	44	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
156	44	48	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
157	56	56	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
158	49	67	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
159	47	69	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
160	46	70	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
161	64	92	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
162	59	164	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
163	56	172	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
164	74	181	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
165	63	189	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
166	70	198	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
167	76	282	3=III	0=No ROP	0=No ROP	3=III	0=No ROP	0=No ROP
168	43	7	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
169	46	8	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
170	39	8	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
171	39	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
172	37	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
173	47	14	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
174	38	15	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
175	34	15	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
176	35	17	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
177	40	18	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
178	38	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with right eye ROP=N due to Lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
179	46	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
180	37	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
181	43	20	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
182	38	21	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
183	38	21	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
184	37	22	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
185	39	27	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
186	38	28	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
187	44	28	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
188	40	35	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
189	57	134	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
190	70	184	3=III	0=No ROP	0=No ROP	3=III	1=Stage 1	1=Stage 1
191	42	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
192	41	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
193	38	14	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
194	40	15	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
195	40	18	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
196	39	19	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
197	48	21	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
198	46	36	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
199	50	43	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
200	53	106	3=III	0=No ROP	0=No ROP	3=III	2=Stage 2	2=Stage 2
201	40	8	3=III	0=No ROP	0=No ROP	3=III	3=Stage 3	3=Stage 3
202	52	66	3=III	0=No ROP	0=No ROP	3=III	3=Stage 3	3=Stage 3
203	116	476	3=III	0=No ROP	0=No ROP	3=III	3=Stage 3	3=Stage 3
204	39	57	3=III	0=No ROP	1=Stage 1	3=III	0=No ROP	0=No ROP
205	47	21	3=III	0=No ROP	1=Stage 1	3=III	2=Stage 2	2=Stage 2
206	35	13	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
207	43	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
208	34	14	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
209	37	18	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
210	37	21	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
211	39	22	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
212	45	24	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
213	44	28	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
214	36	28	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP

Current and previous exam results for infants with right eye ROP=N due to Lowest zone = III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
215	42	28	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
216	43	35	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
217	48	55	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
218	46	77	3=III	1=Stage 1	1=Stage 1	3=III	0=No ROP	0=No ROP
219	44	0	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
220	39	3	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
221	43	5	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
222	42	5	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
223	40	6	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
224	35	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
225	34	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
226	42	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
227	41	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
228	48	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
229	47	7	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
230	37	8	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
231	36	8	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
232	36	8	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
233	37	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
234	40	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
235	36	9	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
236	33	12	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
237	39	12	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
238	36	13	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
239	40	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
240	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
241	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
242	37	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
243	37	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
244	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
245	42	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
246	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
247	47	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
248	43	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
249	36	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
250	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with right eye ROP-N due to Lowest zone - III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
251	35	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
252	38	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
253	35	14	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
254	51	15	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
255	37	16	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
256	42	16	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
257	36	17	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
258	44	17	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
259	42	18	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
260	46	18	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
261	39	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
262	43	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
263	42	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
264	43	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
265	39	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
266	42	21	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
267	40	22	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
268	41	22	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
269	42	24	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
270	46	25	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
271	52	28	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
272	38	29	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
273	48	34	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
274	39	39	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
275	92	163	3=III	1=Stage 1	1=Stage 1	3=III	1=Stage 1	1=Stage 1
276	42	7	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
277	42	9	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
278	45	11	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
279	42	11	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
280	39	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
281	45	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
282	47	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
283	37	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
284	34	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
285	42	14	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
286	41	15	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2

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Current and previous exam results for infants with right eye ROP=N due to lowest zone III for consecutive exams

Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
287	41	15	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
288	43	33	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
289	55	56	3=III	1=Stage 1	1=Stage 1	3=III	2=Stage 2	2=Stage 2
290	34	4	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
291	36	14	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
292	34	21	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
293	36	21	3=III	2=Stage 2	2=Stage 2	3=III	0=No ROP	0=No ROP
294	42	14	3=III	2=Stage 2	2=Stage 2	3=III	1=Stage 1	1=Stage 1
295	39	28	3=III	2=Stage 2	2=Stage 2	3=III	1=Stage 1	1=Stage 1
296	38	2	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
297	48	6	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
298	39	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
299	40	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
300	44	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
301	43	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
302	45	7	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
303	37	8	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
304	40	8	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
305	42	9	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
306	37	9	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
307	46	10	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
308	38	13	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
309	45	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
310	40	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
311	41	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
312	40	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
313	40	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
314	42	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
315	43	14	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
316	46	15	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
317	42	15	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
318	54	21	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
319	46	21	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
320	45	23	3=III	2=Stage 2	2=Stage 2	3=III	2=Stage 2	2=Stage 2
321	35	17	3=III	2=Stage 2	3=Stage 3	3=III	2=Stage 2	2=Stage 2
322	46	49	3=III	3=Stage 3	3=Stage 3	3=III	1=Stage 1	1=Stage 1

Current and previous exam results for infants with right eye ROP=N due to Lowest zone=III for consecutive exams

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Obs	Estimated PMA (weeks) on ROP exam date	Days since previous ROP exam	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right lowest zone of any vessels - previous exam	Right highest stage in lowest zone - previous exam	Right highest stage in any zone - previous exam
323	41	7	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
324	39	14	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
325	38	14	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
326	41	18	3=III	3=Stage 3	3=Stage 3	3=III	2=Stage 2	2=Stage 2
327	41	6	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
328	39	7	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
329	35	7	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
330	44	18	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
331	53	35	3=III	3=Stage 3	3=Stage 3	3=III	3=Stage 3	3=Stage 3
332	54	28	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	1=Stage 1	1=Stage 1
333	38	3	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
334	43	7	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
335	41	9	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
336	42	13	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP
337	50	35	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP	3=III	9=Old scars, but no active ROP	9=Old scars, but no active ROP

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Cases where ROP status changed over time per SUPP10

Center ID number=9 Network number=76591

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
1	07/19/07	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	.	.
2	08/02/07	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	.	.
3	09/26/07	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	.	.	.
4	10/03/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
5	10/11/07	2=II	2=Stage 2	2=Stage 2	Y	Y	0=No surgery this day	.	Y	Threshold (Type I) ROP
6	11/08/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
7	11/19/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
8	02/07/08	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	N	Lowest zone = mature

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	.	.
2	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	.	.
3	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	.	.	.
4	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
5	2=II	2=Stage 2	2=Stage 2	Y	N	0=No surgery this day	.	.	.
6	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
7	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	.	.	.
8	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	.	N	Lowest zone = mature

Center ID number=12 Network number=78572

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
9	02/06/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
10	02/13/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.

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Cases where ROP status changed over time per SUPP10

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
11	02/20/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
12	02/27/07	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
13	03/06/07	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
14	03/13/07	2=II	3=Stage 3	3=Stage 3	Y	N	1=Laser	0=None	Y	ROP surgery
15	03/20/07	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None	Y	ROP surgery
16	03/27/07	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None	Y	ROP surgery
17	04/03/07	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
18	04/17/07	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
9	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
10	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
11	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
12	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
13	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
14	2=II	3=Stage 3	3=Stage 3	Y	N	1=Laser	0=None	Y	ROP surgery
15	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None	Y	ROP surgery
16	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None	Y	ROP surgery
17	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
18	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams

Cases where ROP status changed over time per SUPP10

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Center ID number=16 Network number=82071

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
19	02/08/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
20	02/21/08	2=II	1=Stage 1	1=Stage 1	Y	Y	0=No surgery this day	0=None	Y	Threshold (Type I) ROP
21	03/04/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
22	04/15/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
23	05/06/08	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
24	06/11/08	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
19	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
20	2=II	1=Stage 1	1=Stage 1	Y	N	0=No surgery this day	0=None	.	.
21	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
22	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
23	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
24	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Center ID number=19 Network number=69841

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
25	10/18/05	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
26	11/01/05	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
27	11/15/05	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
28	11/23/05	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
29	12/02/05	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
30	12/09/05	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.

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Cases where ROP status changed over time per SUPP10

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
31	12/16/05	2=II	3=Stage 3	3=Stage 3	N	Y	0=No surgery this day	0=None	Y	Threshold (Type I) ROP
32	03/14/07	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
25	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
26	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
27	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
28	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
29	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
30	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
31	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
32	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Center ID number=22 Network number=50121

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
33	12/14/07	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
34	12/28/07	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
35	01/25/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
36	02/08/08	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
37	02/15/08	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
38	03/01/08	3=III	3=Stage 3	3=Stage 3	N	Y	1=Laser	0=None	Y	Threshold (Type I) ROP

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Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
33	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
34	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
35	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
36	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
37	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
38	3=III	3=Stage 3	3=Stage 3	Y	N	1=Laser	0=None	Y	ROP surgery

Center ID number=23 Network number=67691

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
39	07/17/08	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
40	07/22/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
41	07/28/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
42	08/03/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
43	08/18/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
44	08/25/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
45	09/03/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
46	09/08/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
47	09/15/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
48	09/29/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
49	10/20/08	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
50	11/10/08	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
51	12/01/08	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	N	N	0=No surgery this day	0=None	Y	ROP stage 4 or 5

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Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
39	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
40	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
41	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
42	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
43	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
44	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
45	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
46	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
47	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
48	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
49	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
50	3=III	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
51	4=Mature	4=Stage 4a or 4b	4=Stage 4a or 4b	N	N	0=No surgery this day	0=None	Y	ROP stage 4 or 5

Center ID number=23 Network number=67881

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
52	10/27/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
53	11/03/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
54	11/10/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
55	11/17/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
56	11/24/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
57	12/02/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
58	12/08/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
59	12/15/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.

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Cases where ROP status changed over time per SUPP10

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
60	12/22/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
61	12/29/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
62	01/05/09	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
63	01/12/09	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
64	01/17/09	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
65	01/26/09	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
66	02/09/09	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
67	03/11/09	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
68	03/30/09	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	N	N	0=No surgery this day	0=None	Y	ROP stage 4 or 5

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
52	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
53	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
54	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
55	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
56	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
57	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
58	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
59	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
60	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
61	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
62	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
63	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
64	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.

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Cases where ROP status changed over time per SUPP10

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
65	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
66	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
67	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
68	3=III	4=Stage 4a or 4b	4=Stage 4a or 4b	N	N	0=No surgery this day	0=None	Y	ROP stage 4 or 5

Center ID number=25 Network number=69843

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
69	04/23/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
70	04/30/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
71	05/07/08	2=II	1=Stage 1	1=Stage 1	N	Y	0=No surgery this day	0=None	Y	Threshold (Type I) ROP
72	05/14/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
73	05/21/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
74	05/29/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
75	06/04/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
76	06/11/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
77	06/18/08	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
78	06/25/08	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
79	07/03/08	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
80	07/09/08	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
81	07/15/08	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
82	07/30/08	3=III	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
83	08/06/08	3=III	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
84	08/13/08	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

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Cases where ROP status changed over time per SUPP10

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
69	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
70	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
71	2=II	1=Stage 1	1=Stage 1	N	Y	0=No surgery this day	0=None	Y	Threshold (Type I) ROP
72	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
73	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
74	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
75	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
76	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
77	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
78	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
79	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
80	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
81	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None	.	.
82	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
83	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	N	Lowest zone = III for consecutive exams
84	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Center ID number=25 Network number=69971

Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
85	05/21/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
86	05/29/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
87	06/04/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
88	06/11/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
89	06/25/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.

Cases where ROP status changed over time per SUPP10

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Obs	Examination Date	Left-lowest zone of any vessels	Left-Highest stage in lowest zone	Left-Highest stage in any zone	Left-Plus Disease	Left-Threshold (New Type 1)	Left-Surgery	Left-Post surgical Retinal Detachment	ROP left eye	Reason for ROP determination in left eye
90	07/09/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
91	07/15/08	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
92	07/30/08	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
93	08/06/08	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
94	08/20/08	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
95	09/03/08	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

Obs	Right-lowest zone of any vessels	Right-Highest stage in lowest zone	Right-Highest stage in any zone	Right-Plus Disease	Right-Threshold (New Type 1)	Right-Surgery	Right-Post surgical Retinal Detachment	ROP right eye	Reason for ROP determination in right eye
85	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
86	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
87	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
88	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
89	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
90	2=II	1=Stage 1	1=Stage 1	N	Y	0=No surgery this day	0=None	Y	Threshold (Type I) ROP
91	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None	.	.
92	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
93	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None	.	.
94	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	.	.
95	4=Mature	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None	N	Lowest zone = mature

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status) Infants born before 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of OCGROPEX by sp10anyexam			
OCGROPEX(Was an Exam Performed for ROP?)	sp10anyexam(Any ROP exam (by NG03 status) per SUPP10)		
Frequency	N	Y	Total
N	35	0	35
Y	5	200	205
Total	40	200	240

Table of OCGROP by sp10anyrop			
OCGROP(If YES, was ROP Diagnosed?)	sp10anyrop(Any ROP (stage 1-5) in either eye (by NG03 status) per SUPP10)		
Frequency		Y	Total
	35	0	35
N	69	2	71
Y	1	133	134
Total	105	135	240

Table of OCGHSL by highstagel					
OCGHSL(If ROP, Highest Stage - Left (OS))	highstagel(Left - Highest stage in lowest zone (by NG03 status) per SUPP10)				
Frequency		1=Stage 1	2=Stage 2	3=Stage 3	Total
	105	1	0	0	106
0=No ROP	0	1	0	0	1
1=Stage 1	2	42	1	2	47
2=Stage 2	1	7	45	2	55
3=Stage 3	0	2	4	25	31
Total	108	53	50	29	240

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born before 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of OCGHSR by highstager					
OCGHSR(If ROP, Highest Stage - Right (OD))	highstager(Right - Highest stage in lowest zone (by NG03 status) per SUPP10)				
Frequency	.	1=Stage 1	2=Stage 2	3=Stage 3	Total
.	105	0	1	0	106
0=No ROP	3	1	0	0	4
1=Stage 1	3	41	2	2	48
2=Stage 2	1	7	44	3	55
3=Stage 3	0	2	3	22	27
Total	112	51	50	27	240

Table of OCGLZL by lowzonel					
OCGLZL(If ROP, Lowest Zone - Left (OS))	lowzonel(Left - Lowest zone with ROP (by NG03 status) per SUPP10)				
Frequency	.	1=I	2=II	3=III	Total
.	105	0	2	0	107
1=I	0	4	2	1	7
2=II	1	4	103	1	109
3=III	2	2	3	10	17
Total	108	10	110	12	240

Table of OCGLZR by lowzoner					
OCGLZR(If ROP, Lowest Zone - Right (OD))	lowzoner(Right - Lowest zone with ROP (by NG03 status) per SUPP10)				
Frequency	.	1=I	2=II	3=III	Total
.	107	0	1	1	109
P=Permanently missing	1	0	0	0	1
1=I	0	4	4	1	9
2=II	3	6	98	1	108
3=III	1	2	2	8	13
Total	112	12	105	11	240

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born before 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of OCGPLUSL by plusdisl

OCGPLUSL(If ROP, Plus Disease - Left (OS))	plusdisl(Left - Plus disease in exam with highest stage per SUPP10)			
Frequency		N	Y	Total
	105	2	0	107
N	3	110	0	113
Y	0	11	9	20
Total	108	123	9	240

Table of OCGPLUSR by plusdisr

OCGPLUSR(If ROP, Plus Disease - Right (OD))	plusdisr(Right - Plus disease in exam with highest stage per SUPP10)			
Frequency		N	Y	Total
	105	2	0	107
N	7	107	0	114
Y	0	10	9	19
Total	112	119	9	240

Table of NG3THRLT by sp10threshl

NG3THRLT(+1/02 thresh ROP at any time - left eye)	sp10threshl(Left - Threshold ROP (by NG03 status) per SUPP10)		
Frequency		Y	Total
	107	0	107
*	1	0	1
N	112	3	115
Y	8	9	17
Total	228	12	240

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exam is prior to NG03 status)
Infants born before 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of NG3THRRT by sp10threshr

NG3THRRT(+1/02 thresh ROP at any time - right eye)	sp10threshr(Right - Threshold ROP (by NG03 status) per SUPP10)		
Frequency		Y	Total
	107	0	107
*	1	0	1
N	112	2	114
Y	9	9	18
Total	229	11	240

Table of NG3ABLLT by surgl

NG3ABLLT(+1/02 Retinal ablation performed - left)	surgl(Left - ROP surgery (by NG03 status) per SUPP10)		
Frequency	.	1=Laser	Total
	107	0	107
*	0	1	1
N	116	11	127
Y	0	5	5
Total	223	17	240

Table of NG3SRGLT by surgl

NG3SRGLT(+1/02 Surgery performed - Left)	surgl(Left - ROP surgery (by NG03 status) per SUPP10)		
Frequency	.	1=Laser	Total
.	107	0	107
P	1	0	1
0=None	108	1	109
1=Laser therapy	7	16	23
Total	223	17	240

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born before 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of NG3ABLRT by surgr			
NG3ABLRT(+1/02 Retinal ablation performed - Right)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)		
Frequency	.	1=Laser	Total
	107	0	107
*	0	1	1
N	113	15	128
Y	0	4	4
Total	220	20	240

Table of NG3SRGRT by surgr			
NG3SRGRT(+1/02 Surgery performed - Right)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)		
Frequency	.	1=Laser	Total
.	107	0	107
P	1	0	1
0=None	108	1	109
1=Laser therapy	4	19	23
Total	220	20	240

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of OCGROPEX by sp10anyexam			
OCGROPEX(Was an Exam Performed for ROP?)	sp10anyexam(Any ROP exam (by NG03 status) per SUPP10)		
Frequency	N	Y	Total
N	158	1	159
Y	18	873	891
Total	176	874	1050

Table of OCGROP by sp10anyrop			
OCGROP(If YES, was ROP Diagnosed?)	sp10anyrop(Any ROP (stage 1-5) in either eye (by NG03 status) per SUPP10)		
Frequency		Y	Total
	159	0	159
N	335	24	359
Y	21	511	532
Total	515	535	1050

Table of NG3STG3 by sp10stage3			
NG3STG3(Yes, ROP - reach stage 3 or worse)	sp10stage3(Stage 3 or worse in either eye (by NG03 status) per SUPP10)		
Frequency		Y	Total
	516	2	518
N	380	13	393
Y	7	132	139
Total	903	147	1050

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table of NG3PLUS by sp10plusdis			
NG3PLUS(Yes, ROP - plus disease in either eye)	sp10plusdis(Plus disease in either eye (by NG03 status) per SUPP10)		
Frequency		Y	Total
	518	0	518
N	446	6	452
Y	9	71	80
Total	973	77	1050

Table 1 of surgl by surgr Controlling for NG3RTABL=					
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	518	0	0	0	518
1=Laser	0	0	0	0	0
1&6=Laser and Avastin	0	0	0	0	0
3=Both laser/cryo	0	0	0	0	0
6=Other	0	0	0	0	0
Total	518	0	0	0	518

Table 2 of surgl by surgr Controlling for NG3RTABL=N					
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	441	0	0	0	441
1=Laser	0	0	0	0	0
1&6=Laser and Avastin	0	0	0	0	0
3=Both laser/cryo	0	0	0	0	0
6=Other	0	0	0	2	2
Total	441	0	0	2	443

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table 3 of surgl by surgr					
Controlling for NG3RTABL=Y					
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	9	3	0	0	12
1=Laser	1	73	0	0	74
1&6=Laser and Avastin	0	1	0	0	1
3=Both laser/cryo	0	0	2	0	2
6=Other	0	0	0	0	0
Total	10	77	2	0	89

Table 1 of surgl by surgr					
Controlling for NG3SCLRL=					
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	518	0	0	0	518
1=Laser	0	0	0	0	0
1&6=Laser and Avastin	0	0	0	0	0
3=Both laser/cryo	0	0	0	0	0
6=Other	0	0	0	0	0
Total	518	0	0	0	518

Table 2 of surgl by surgr					
Controlling for NG3SCLRL=N					
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	450	3	0	0	453
1=Laser	1	71	0	0	72
1&6=Laser and Avastin	0	1	0	0	1
3=Both laser/cryo	0	0	2	0	2
6=Other	0	0	0	2	2
Total	451	75	2	2	530

Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

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The FREQ Procedure

Table 3 of surgl by surgr

Controlling for NG3SCLRL=Y

surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	0	0	0	0	0
1=Laser	0	2	0	0	2
1&6=Laser and Avastin	0	0	0	0	0
3=Both laser/cryo	0	0	0	0	0
6=Other	0	0	0	0	0
Total	0	2	0	0	2

Table 1 of ropleftreason by roprightreason

Controlling for NG3OPHTH=.

ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)					
Frequency	.	Threshold (Type I) ROP	ROP surgery	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	159	0	0	0	0	159
Threshold (Type I) ROP	0	0	0	0	0	0
ROP surgery	0	0	0	0	0	0
Lowest zone = mature	0	0	0	0	0	0
Lowest zone = III for consecutive exams	0	0	0	0	0	0
Total	159	0	0	0	0	159

Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

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The FREQ Procedure

Table 2 of ropleftreason by roprightreason						
Controlling for NG3OPHTH=1=Determined, favorable both eyes						
ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)					
Frequency	.	Threshold (Type I) ROP	ROP surgery	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	88	3	0	1	4	96
Threshold (Type I) ROP	0	7	1	0	0	8
ROP surgery	0	0	1	0	0	1
Lowest zone = mature	0	0	0	107	1	108
Lowest zone = III for consecutive exams	6	0	0	2	101	109
Total	94	10	2	110	106	322

Table 3 of ropleftreason by roprightreason						
Controlling for NG3OPHTH=2=Determined, severe ROP either eye						
ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)					
Frequency	.	Threshold (Type I) ROP	ROP surgery	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	3	4	1	0	0	8
Threshold (Type I) ROP	0	42	2	0	0	44
ROP surgery	0	2	20	0	0	22
Lowest zone = mature	0	0	0	0	0	0
Lowest zone = III for consecutive exams	0	0	0	0	0	0
Total	3	48	23	0	0	74

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Cross-tabs comparing ROP data from NG03 vs. SUBP10 (exams prior to NG03 status) Infants born on or after 1/1/2006 and surviving to 12 hours

The FREQ Procedure

Table 4 of ropleftreason by roprightreason						
Controlling for NG3OPHTH=3=Undetermined						
ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)					
Frequency	.	Threshold (Type I) ROP	ROP surgery	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	451	0	0	2	1	454
Threshold (Type I) ROP	1	7	0	0	0	8
ROP surgery	0	0	0	0	0	0
Lowest zone = mature	2	0	0	8	0	10
Lowest zone = III for consecutive exams	2	0	0	1	20	23
Total	456	7	0	11	21	495

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours
Surgery in left and right eye (per SUPP10) where retinal ablation=N per NG03

The FREQ Procedure

Table of surgl by surgr			
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)		
Frequency	.	6=Other	Total
.	441	0	441
6=Other	0	2	2
Total	441	2	443

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours
Surgery in left and right eye (per SUPP10) where retinal ablation=Y per NG03

The FREQ Procedure

Table of surgl by surgr				
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)			
Frequency	.	1=Laser	3=Both laser/cryo	Total
.	9	3	0	12
1=Laser	1	73	0	74
1&6=Laser and Avastin	0	1	0	1
3=Both laser/cryo	0	0	2	2
Total	10	77	2	89

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours
Surgery in left and right eye (per SUPP10) where scleral buckle or vitrectromy =N per NG03

The FREQ Procedure

Table of surgl by surgr

surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)				
Frequency	.	1=Laser	3=Both laser/cryo	6=Other	Total
.	450	3	0	0	453
1=Laser	1	71	0	0	72
1&6=Laser and Avastin	0	1	0	0	1
3=Both laser/cryo	0	0	2	0	2
6=Other	0	0	0	2	2
Total	451	75	2	2	530

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours
Surgery in left and right eye (per SUPP10) where scleral buckle or vitrectromy =Y per NG03

The FREQ Procedure

Table of surgl by surgr		
surgl(Left - ROP surgery (by NG03 status) per SUPP10)	surgr(Right - ROP surgery (by NG03 status) per SUPP10)	
Frequency	1=Laser	Total
1=Laser	2	2
Total	2	2

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours

ROP reason in left and right eye (per SUPP10) where ROP status is '1=Determined, favorable in both eyes' per NG03

The FREQ Procedure

Table of ropleftreason by roprightreason

ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)					
Frequency	.	Threshold (Type I) ROP	ROP surgery	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	88	3	0	1	4	96
Threshold (Type I) ROP	0	7	1	0	0	8
ROP surgery	0	0	1	0	0	1
Lowest zone = mature	0	0	0	107	1	108
Lowest zone = III for consecutive exams	6	0	0	2	101	109
Total	94	10	2	110	106	322

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)

Infants born on or after 1/1/2006 and surviving to 12 hours

ROP reason in left and right eye (per SUPP10) where ROP status is '2=Determined, severe ROP in either eye' per NG03

The FREQ Procedure

Table of ropleftreason byroprightreason

ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)			
Frequency	.	Threshold (Type I) ROP	ROP surgery	Total
.	3	4	1	8
Threshold (Type I) ROP	0	42	2	44
ROP surgery	0	2	20	22
Total	3	48	23	74

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Cross-tabs comparing ROP data from NG03 vs. SUPP10 (exams prior to NG03 status)
Infants born on or after 1/1/2006 and surviving to 12 hours
ROP reason in left and right eye (per SUPP10) where ROP status is '3=Undetermined' per NG03

The FREQ Procedure

Table of ropleftreason by roprightreason

ropleftreason(Reason for ROP determination in left eye)	roprightreason(Reason for ROP determination in right eye)				
Frequency	.	Threshold (Type I) ROP	Lowest zone = mature	Lowest zone = III for consecutive exams	Total
.	451	0	2	1	454
Threshold (Type I) ROP	1	7	0	0	8
Lowest zone = mature	2	0	8	0	10
Lowest zone = III for consecutive exams	2	0	1	20	23
Total	456	7	11	21	495

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ++++Duke site visit++++++
Date: Thursday, August 27, 2009 11:55:03 AM

The other more practical concern is that we would miss your expertise in ROP when reviewing the charts.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 27, 2009 11:53 AM
To: Das, Abhik
Cc: Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: Re: ++++Duke site visit++++++

I am not going to decide for another day or so. I know that presence is important, but this needs to get done

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Huitema, Carolyn Petrie <petrie@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Thu Aug 27 11:47:31 2009
Subject: RE: ++++Duke site visit++++++

Rose:

(b) (6) [redacted]. We can do the site visit without you if you want. Of course, we likely won't command the same level of deference and responsiveness as you would!

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 27, 2009 11:38 AM
To: Das, Abhik; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: ++++Duke site visit++++++

Abhik, Carolyn and Kris-
(b) (6) [redacted]

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(b) (6) may not be able to attend the Duke site visit.

I am confident that RTI can obtain the appropriate information. I can get a "report" from you (based on the agenda that Kris already put together) and then formulate recommendations as needed. I think there is urgency to do this next week to sort out the SUPPORT ROP data.

Would this be ok for you to go without me?

Let me know

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale; Susie Buchter; anthony_piazza@oz.ped.emory.edu
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Wednesday, August 26, 2009 3:15:31 PM
Attachments: SUPPORT_BPD_queries_Center_9_(8.26.09).rtf

Rose,
I think we have satisfied all the BPD questions except for 3 charts (have been requested and should have this week). I am in the process of reviewing to make sure that all PH01's that should be entered, have been entered and not just coded on the NG07. Do not have any new nesws on the ROP front. Will keep working on it.
Ellen

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 11:56 AM
To: Hale, Ellen; Barbara Stoll; Ellen Hale; Susie Buchter
Cc: Gantz, Marie
Subject: FW: SUPPORT

Hi,

Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:02 PM
To: 'Barbara Stoll'; ellen_hale@oz.ped.emory.edu; 'Susie Buchter'; 'Ira Adams-Chapman'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,

We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07C Eligible for challenge
N	Y	N	N	.	RA	O2	None	O2	.	Y	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11@status RA by NC/vent/CPAP	NG07@status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	Chart off site and should have soon.

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11@status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6)) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
N	?	N	N	.	RA	RA	None	RA	.

PH01 Eligible for challenge	NG07C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
Y		.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).			Data entry error; SUPP11 corrected

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	NG07-C Eligible for challenge	NG07-C Eligible for challenge
N	Y	N	N	.	RA	O2	RA(<=.5)	O2	.	Y	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
N	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution Center notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	Chart off site and should have soon.

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	NG07-C Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	Y

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Number of days on O2 @36wks per NG07 (b) (6) is greater than DOL @36wks (b) (6)		NG07 corrected—addition error

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	Y	.	.	O2	.	.	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07 c Eligible for challenge	PH01 RA to challenge	SP11 @status Vent/CPAP	SP11 @status NoVent/CPAP	NG07 @status NoVent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC Vent/CPAP	NG07 @status RA by NC Vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			SUPP11 entered— PH01 corrected

Center ID number=9=Emory University Network number (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07 c Eligible for challenge	PH01 RA to challenge	SP11 @status Vent/CPAP	SP11 @status NoVent/CPAP	NG07 @status NoVent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC Vent/CPAP	NG07 @status RA by NC Vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @36wks Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @36wks Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
Y	Y	Y	Y	.	O2	O2	None	.	.	N	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

	Number of days on O2 @36wks per NG07 (b) (6) is greater than DOL @36wks (b) (6)		NG07 corrected

Center ID number=9=Emory University Network numbe (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On Support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 to Eligible for challenge	PH02RA Passed challenge	SP11 @36wks Vent/CPAP	SP11 @36wks NC/vent/CPAP	NG07 @36wks NC/vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks RA by NC/vent/CPAP	NG07 @36wks RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @36wks O2 by NC	NG07 @36wks O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6)) per NG03 but SUPP11 forms are only entered through (b) (6) .			Chart off site and should have soon.

Center ID number=9=Emory University Network numbe (b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On Support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 to Eligible for challenge	PH02RA Passed challenge	SP11 @36wks Vent/CPAP	SP11 @36wks NC/vent/CPAP	NG07 @36wks NC/vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks RA by NC/vent/CPAP	NG07 @36wks RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @36wks O2 by NC	NG07 @36wks O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks on support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

PH01 Eligible for challenge	NG07 Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	RA	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution center notes
N	.	N	Infant left hospital on (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks on support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07 Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07 c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
N	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6)) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

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SUPPORT BPD Queries for Center 9-Emory University

NG07-c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NG/vent/CPAP	NG07 @status NG/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NG/vent/CPAP	NG07 @status RA by NG/vent/CPAP
Y	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks on support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01RA @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01RA @36wks O2/RA(flow) by NC	b1 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NG/vent/CPAP	NG07 @status NG/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NG/vent/CPAP	NG07 @status RA by NG/vent/CPAP
N	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

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From: Finer, Neil
To: "Wally Carlo, M.D."; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials
Date: Wednesday, August 26, 2009 12:46:21 PM

I agree Wally
I am asking are we powered for this outcome – This strata is bigger than almost any previous trial. That is my question to Abhik.

Neil N. Finer, M.D.
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, August 26, 2009 7:00 AM
To: Das, Abhik; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

NEJM has published specific requirements necessary for reporting subgroups results. Only if we meet those criteria, should we include it in the paper. As we did not pre-specify the subgroup analysis and are not powered for it, we need to be very thoughtful on whether we should report it of highlight it.

Wally Carlo, M.D.
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Phone: 205 934 4680
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Cell: 205 266(b) (6)

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, August 26, 2009 8:51 AM
To: Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Rich, Wade
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

I may have missed it, but I don't see any explicit mention in the protocol of our intent to report outcomes by GA strata. So, I would say that while we can certainly report this and comment on it, we are perhaps better off not playing it up too much, beyond saying that it is a strongly suggestive result. NEJM would also likely not allow us to include it in the abstract.

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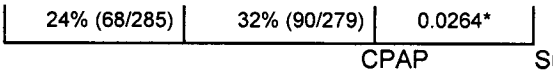
Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 25, 2009 5:59 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Das, Abhik; Rich, Wade
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Hello Everyone
It appears we can find whatever definition we want.
The problem using the Physiologic as the primary is that we did not use Physiologic BPD to determine the sample size or postulated improvement. The protocol is obviously unclear. I would suggest that we report both but that we stick to BPD defined as Oxygen at 36 weeks as the primary as this is the only way to allow others to interpret our data and guys like me who do the meta analyses to combine trials.
There was simply too much interpretation required for the Physiologic and no agreed to standards as to how one would define an individual child – ie on NC at 1 lpm RA ? BPD or NO? NC at 2 LPM BPD or NO?. Nasal CPAP RA – BPD or NO?
No other study has done the oxygen withdrawal in other prospective trials. While the Physiologic will no doubt provide some useful info – I would not want this trial to depend on it. I am also unsure how you power a study using one outcome and then use that data to measure the effect of another.

The other major result – and we have significance without manipulation – is the death rate in the small strata.
This is a major difference and larger than any BPD outcome. This strata is larger than any trial of this population for respiratory interventions. Abhik What will be allowed to say?? 24-25 weeks strata



Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, August 25, 2009 2:42 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Das, Abhik
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

This is also from the current protocol (page 21)

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 25, 2009 5:40 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'

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Cc: Gantz, Marie; Das, Abhik
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Rose
This is how I read the Primary
Neil

Neil N. Finer, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 25, 2009 1:35 PM
To: 'Wally Carlo, M.D.'; Finer, Neil
Cc: Gantz, Marie; Das, Abhik
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

The protocol states:

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in
infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

In the protocol physio def is listed as a predefined secondary outcome

Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, August 25, 2009 4:34 PM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Neil:

I just checked the protocol. The primary outcome was death/BPD (with phys def). There is a secondary also for BPD by phys def. I think it would be best to report this as well as BPD by clinical needs as well as other measures of O2 or vent needs. All of this could be the part of the main analysis.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 25, 2009 10:46 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; Marsha Sumner
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

I have attached an Abstract for everyone – Very preliminary
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 25, 2009 5:33 AM
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu; Finer, Neil
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Hi,
Neil will give a SUPPORT update at the beginning of the call today promptly at 3 PM!!!

Thanks
Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 25, 2009 8:26 AM
To: Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu;

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ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu; nfiner@ucsd.edu
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: Confidential: Steering Committee Call Tuesday and Materials

All – A reminder for our call today. Please see updated agenda below and attached materials.

UPDATED: Steering Committee Conference Call Agenda 08/25/2009

1. Hydrocortisone protocol presentation (3-3:40) – Presentation and protocol attached
2. SUPPORT Update – Dr. Finer – materials attached (confidential)
3. Vitamin E Update
4. NEST Update
5. FU Bayley III motor component
6. New business

From: Cunningham, Meg
Sent: Thursday, August 20, 2009 12:43 PM
To: [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; ifrantz@tuftsmedicalcenter.org; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; 'mca113@northwestern.edu'; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; 'jon.e.tyson@uth.tmc.edu'; 'Michael Cotten'; 'rohls@salud.unm.edu'; 'Bradley.Yoder@hsc.utah.edu'; 'ambal@uab.edu'; Wallace, Dennis
Cc: Smith, Nancy M; 'jwaidne@emory.edu'; 'Brenda Vecchio'; 'gonza025@mc.duke.edu'; 'Archer, Stephanie (NIH/NICHD) [E]'; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; 'msumner@peds.uab.edu'
Subject: Steering Committee Call Tuesday

Dear All -

The next standing Steering Committee call is scheduled for Tuesday, August 25th at 3 PM ET.

Please Dial:
Outside the USA 1-203-310(b) (6)
or Within the USA 866-675(b) (6)
Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 08/25/2009

7. Hydrocortisone protocol presentation (3-3:40)
8. New business

Thanks!
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org

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From:	Walsh, Michele
To:	Finer, Neil; Cunningham, Meg; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc:	Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject:	RE: SUPPORT call
Date:	Tuesday, August 25, 2009 4:07:07 AM

Congrats Neil: this is outstanding! Michele

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Mon 8/24/2009 12:21 PM
To: Finer, Neil; 'Cunningham, Meg'; 'alaptook@WIHRI.org'; 'Bradley Yoder'; 'Das, Abhik'; 'Gantz, Marie'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'Roger.Faix@hsc.utah.edu'; 'Wallace, Dennis'; 'Wally Carlo, M.D.'; Rich, Wade
Cc: 'Newman, Jamie'; 'sharon.gough@hsc.utah.edu'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Martinez, Fernando; 'Huitema, Carolyn Petrie'; 'msumner@peds.uab.edu'; 'Zaterka-Baxter, Kristin'; 'Starlett Williams'; 'Irene, Amanda'
Subject: RE: SUPPORT call

Hello Everyone
I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik.
Please find the basic demographic tables and the outcome of BPD and death etc. You will note that Death/BPD using the need for oxygen at 36 weeks as the postulated primary – because that was the data we based the study on – is significant both unadjusted and adjusted. Note that BPD is also less for the Low SpO2 group – but for that study, we need ROP which we are still waiting for.
Congratulations on a study well done to you all and the coordinators, and RTI
Wally Wade and I will be at RTI a week today to review all the data and I have already started the first paper.
Be well
Neil

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Facsimile: 619.543.3812

From: Finer, Neil
Sent: Tuesday, August 11, 2009 7:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Here are the Tables we sent to Marie

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Telephone: 619.543-3759
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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

Tuesday, 8/11
11:00am ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
[redacted](b) (6)

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From: Susan Hintz
To: pbarnes@stanford.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT MRI project
Date: Tuesday, August 25, 2009 12:27:08 PM

Hi Pat

I know you have been going crazy with all the NICHD projects and everything else in your life and work. I realize the Hypothermia MRI project was much more involved and complex than originally planned. I also realize that there have been suggestions made on the hypothermia conference calls about further "re-readings" and proceeding with intrarater reliability reads at this point. I think the results of the hypothermia MRI project will be truly interesting and important, and I am excited to see the final findings. However, as you know, the SUPPORT (premie) MRI project has been completely on hold for many months now, and we must move forward. I know you have been put in the middle of all this, and you also have many other demands on your time. I have spoken with Rose Higgins, and she agrees that it is time to let you truly and completely set aside the hypothermia project and move full steam forward on SUPPORT. So, after the Friday hypothermia conference call (which hopefully will wrap up the final questions about the readings), you will not be dealing with hypothermia at all in the near future. It may be that at some point (after all is complete with SUPPORT), you may be engaged to do re-reads, but not until SUPPORT is complete.

The SUPPORT MRI reading is critical at this point, because all of the CUS central reads are just about completed. The main trial results (i.e., whether the ventilation and oxygenation target interventions impacted the rates of BPD and other short term outcomes) will be coming out very soon - and they are likely to be very interesting and high profile. So, it is crucial that we get these important secondary analyses out and in the public eye as soon as possible.

I would envision the first abstract from the neuroimaging component of SUPPORT to be broad in scope - just a report of brain injuries on CUS and MRI, perhaps very preliminary comparison of late CUS and MRI in terms of findings. We do not yet have neurodevelopmental follow-up data at 18-22 months, so that will be an analysis for later. In order to make the deadline for the Pediatric Academic Societies meeting late breaker abstract (which would be a high-impact meeting in which to present the report, and would also be the same meeting as the main trial results are reported), realistically all SUPPORT neuroimaging needs to be read by beginning of November. That is even pushing it, and assumes that I will be sending back the readings as they are done, dealing with data entry questions in "real time" and setting up preliminary analysis plans in the next month or so with statisticians. This will mean you would need to read ~50-55 MRIs each week. I will commit to set aside as much time in my schedule whenever you want me to help (i.e., early mornings, evenings, etc) to help score and get this done. Is this possible?

Please let me know what you think - thanks Pat

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Susan

--

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From: Susan Hintz
To: mcunningham@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; joa@rti.org; Qing Yao; Jamie Newman
Subject: Data requests, tracking, etc re: SUPPORT neuroimaging
Date: Tuesday, August 25, 2009 1:35:34 AM
Attachments: MasterMRIFU_20090610.xls

Hi Meg, Qing, Jenny, Jamie, Rose, Abhik,

With the second central US reading for SUPPORT just completed, we now need to tackle the issue of what we have completed, what we have left to do, what is missing, etc. We need this to plan how the rest of the CUS readings will be done, the timeline, and analysis plans. **I would like for us to have something completed for late breakers PAS - and I think realistically we need to say all readings must be done and input by beginning of November, providing we have been inputting the central reader data as it comes in.** (And also provided we start data cleaning and plan for analysis strategy.)

In addition, thinking about how we will wrap up the neuroimaging readings and analysis has reminded me to ask a separate series of questions about the 18-22 mo follow-up and school-age follow-up.

So here it goes -

1) Characterization of CUS studies: expected, done, left to do, plans for remaining reading.

a. In order to plan how many days we need to read with Dr. Bulas and Dr. Slovis, we will need the following info:

i. How many total CUS are expected in the entire study? (All MRI01 forms should be submitted by now, so we should know this number at this point.)

ii. Are any of these "expected" CUS still not sent to RTI by the sites?

iii. How many CUS were read in the first central reading by DB, how many by TS?

iv. How many total CUS were read in the second central reading by DB, how many by TS?

v. How many patients have BOTH early and late CUS? How many of these have been completely read by both DB and TS?

vi. How many have COMPLETE neuroimaging (early CUS, late CUS, MRI)

b. Of course we want every CUS we can get, but the most important group for the study as a whole is the group that has all neuroimaging. So, we should be most aggressive about getting the CUS that are missing in that group.

2) Setting up more readings

a. As we discussed at the central reading, we should **move forward now with arranging separate dates for RTI to go out to Dr. Slovis and Dr. Bulas to finish up** the readings- and I think Meg may already be looking at dates for her and Amanda to vist with Dr. Bulas. I believe Julie will be going out to see Dr. Slovis? In any case, I

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recommend nailing down a FEW DATES NOW for the next 4 -6 weeks (even if it is a day here and a day there).

3) More data requests, but related to above questions:

a. The big spreadsheet Meg has and I want: Meg has a very nice spreadsheet with what I believe is ALL patients who were enrolled in SUPPORT Neuroimaging who have ANY CUS. Could I have an updated version of that electronically?

i. Will the "updated version" I receive be final and complete? In other words, will all the MRI01 data be in by now.

ii. Also, that spreadsheet indicates if Early or Late US and MRI were doneŠbut not whether they have been received. I really don't want to make that spreadsheet more cumbersome, so don't add columns, you can just answer 1.b above.

b. "MasterMRIFU" data sheet: Jenny Auman made a really nice spreadsheet for me with all sorts of information pertinent to the neuroimaging and follow-up issues. Jenny - could I have an updated version? **I am attaching the June 10 version just to show you which spreadsheet I mean.**

c. Pertinent to questions 1.f - looking at the June 10 version of the MasterMRIFU list, it seems that there are only 12 patients with an early CUS and a successful MRI, but NO late CUSŠthis is a group (and of course there may be more than 12 now) that we should really try to understand. As I said above, the most important group we should focus on is the group that have ALL neuroimaging, so if they are missing a late CUS but they actually have one somewhere, we should try to snag it.

4) Tracking for extended follow-up - I know a lot of questions will come up about the details of this and the $$ involved as we move toward the follow-up of this group. So here are a few questions and comments -

a. REMINDERS to sites? As you know, we did remind PI's about the 3-4 year tracking for the school age follow-up on the FU PI conference call. However, can we do something more formal - or are you already doing that? Can you - or are you already planning to - send out an email 3 months before the 3-4 year window opens to remind about the form, then again at 3 _ years IF the form is not yet completed? I know that sites don't like to be "bugged", but if they understand that tracking reimbursement is LINKED to completion of that form, it may be better tolerated.

i. BTW, from the MasterMRIFU spreadsheet I think we have **68 or 69 subjects who have already have their window open for 3-4 year tracking! 9 or 10 patients will have that window CLOSED by the end of this month!** Are the tracking forms in on those yet?

b. $$ for tracking between 18-22 months and 3-4 years: Rose, can you tell me how much was the FINAL budgeted for the contacts between 18-22 months and 3-4 years? We had said in the original budget that it would be 2 one-hour contacts at $35/hr, but I think that was revised upward. Also, from a process perspective, when are those funds released to sites? As soon as they complete the 3-4 year tracking form? Or when the patient will reach 3-4 years IF the tracking form has been completed?

c. How will the later tracking funds will be distributed and contact attempts "verified"? In the protocol, we originally budgeted four 2 hour tracking contacts (total 8 hours of

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tracking contact at $35/hr) for tracking between 3-4 years and the school age follow-up visit. We now have a mechanism in place to "track the tracking" at 3-4 years. But what should we do for tracking between 3-4 and the school age visit? Just a reminder email at 5 _ years? And are we just distributing the tracking funds without "verification"?

5) Data "cleaning" and analysis:

a. Qing - we could probably start talking about starting some data clean up and setting up analyses so we can be ahead of the game.

i. I have a few ideas for cleaning up the data. For instance, we will need to look at "normal" and make sure there really are NO things marked on the form or comments made. Also, we will need to search the comments for any mention of cerebellar or cerebellum because some abnormalities in that area were not so easily categorized. Also a few other things, but I will make a list of things I am thinking about, and you can also tell me what you think.

ii. As for how we will look at the data and prelim analysis - should I put together some mock data tables?

Thanks again all! I am sure I have forgotten a lot, but that's it for now.

THANKS for all your help and great work!

Susan

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Center	Birth Date	Network	Enrolled	Head US #1 (Y/N)	Head US #2 (Y/N)	SuccesMRI (Y/N)	Date of Brain MRI	18 - 22 mo FU OPEN	18 - 22 mo FU CLOSE	18-22 mo FU DONE (date)	18-22 mo FU status	3-4 yr OPEN	Have SEF01?	3-4 yr Contact Made?	3-4 yr Status	6-7 yr OPEN	6-7 yr CLOSE
15	(b) (6)		Y	Y	N	Y	7/1/2005	2/6/2007	6/21/2007	4/30/2007	Visit comp	5/9/2008				5/9/2011	5/8/2012
15			Y	Y	Y	Y	8/1/2005	2/14/2007	6/29/2007		Lost to folu	5/14/2008				5/14/2011	5/13/2012
22			Y	Y	Y	Y	10/26/2005	5/5/2007	9/20/2007	5/10/2007	Visit comp	7/27/2008				7/27/2011	7/26/2012
22			Y	Y	Y	Y	10/26/2005	5/5/2007	9/20/2007	5/10/2007	Visit comp	7/27/2008				7/27/2011	7/26/2012
22			Y	Y	Y	Y	11/3/2005	5/19/2007	10/4/2007	6/7/2007	Visit comp	8/16/2008				8/16/2011	8/15/2012
22			Y	Y	Y	Y	11/17/2005	5/19/2007	10/4/2007	6/7/2007	Visit comp	8/16/2008				8/16/2011	8/15/2012
22			Y	Y	Y	Y	11/15/2005	5/26/2007	10/11/2007	6/25/2007	Visit comp	8/30/2008				8/30/2011	8/29/2012
22			Y	Y	Y	Y	11/15/2005	5/30/2007	10/15/2007	6/25/2007	Visit comp	8/30/2008				8/30/2011	8/29/2012
22			Y	Y	Y	Y	11/21/2005	6/1/2007	10/16/2007	7/16/2007	Visit comp	9/4/2008				9/4/2011	9/3/2012
22			Y	Y	Y	Y	2/9/2006	8/14/2007	12/29/2007	9/28/2007	Visit comp	10/24/2008				10/24/2011	10/23/2012
21			Y	Y	Y	Y	6/13/2006	11/30/2007	4/14/2008		Lost to folu	3/2/2009				3/1/2012	3/1/2013
3			Y	Y	Y	Y	6/27/2006	12/17/2007	5/2/2008	3/20/2008	Visit comp	3/14/2009				3/13/2012	3/13/2013
3			Y	Y	N	Y	6/30/2006	12/17/2007	5/2/2008	3/20/2008	Visit comp	3/14/2009				3/13/2012	3/13/2013
3			Y	Y	Y	Y	6/23/2006	1/11/2008	5/26/2008	1/31/2008	Visit comp	3/31/2009				3/30/2012	3/30/2013
14			Y	Y	Y	Y	6/23/2006	1/12/2008	5/27/2008	2/27/2008	Visit comp	4/6/2009	Y	Y	Family is pl	4/5/2012	4/5/2013
14			Y	Y	Y	Y	6/23/2006	1/12/2008	5/27/2008	2/27/2008	Visit comp	4/6/2009	Y	Y	Family is pl	4/5/2012	4/5/2013
3			Y	Y	Y	Y	6/14/2006	1/4/2008	5/19/2008	3/6/2008	Visit comp	4/7/2009				4/6/2012	4/6/2013
18			Y	Y	Y	Y	6/7/2006	1/8/2008	5/23/2008	4/24/2008	Visit comp	4/9/2009	Y	Y	Family is pl	4/8/2012	4/8/2013
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18			Y	Y	Y	Y	7/8/2006	1/19/2008	6/3/2008	5/5/2008	Visit comp	4/14/2009				4/13/2012	4/13/2013
3			Y	Y	Y	Y	8/21/2006	1/28/2008	6/12/2008	4/1/2008	Visit comp	4/20/2009				4/19/2012	4/19/2013
4			Y	Y	Y	Y	7/10/2006	2/5/2008	6/20/2008	2/7/2008	Visit comp	4/21/2009				4/20/2012	4/20/2013
15			Y	Y	Y	Y	7/19/2006	1/22/2008	6/6/2008	2/27/2008	Visit comp	4/27/2009				4/26/2012	4/26/2013
15			Y	Y	Y	Y	7/11/2006	2/2/2008	6/17/2008	3/13/2008	Visit comp	5/1/2009				4/30/2012	4/30/2013
18			Y	Y	Y	Y	7/26/2006	2/5/2008	6/20/2008	2/13/2008	Visit comp	5/1/2009				4/30/2012	4/30/2013
14			Y	Y	Y	Y	7/11/2006	2/5/2008	6/20/2008	3/11/2008	Visit comp	5/11/2009	Y	Y	Family dec	5/10/2012	5/10/2013
3			Y	Y	Y	Y	7/27/2006	2/9/2008	6/24/2008	3/6/2008	Visit comp	5/13/2009				5/12/2012	5/12/2013
3			Y	Y	Y	Y	8/17/2006	3/4/2008	7/19/2008	5/15/2008	Visit comp	5/27/2009				5/26/2012	5/26/2013
18			Y	Y	Y	Y	8/23/2006	3/5/2008	7/20/2008		Another Ce	6/3/2009				6/2/2012	6/2/2013
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16			Y	Y	Y	Y	9/1/2006	3/18/2008	8/2/2008	4/18/2008	Visit comp	6/11/2009				6/10/2012	6/10/2013
3			Y	Y	Y	Y	8/14/2006	3/13/2008	7/28/2008	4/1/2008	Visit comp	6/15/2009				6/14/2012	6/14/2013
14			Y	Y	Y	Y	8/30/2006	3/16/2008	7/31/2008	5/20/2008	Visit comp	6/15/2009				6/14/2012	6/14/2013
14			Y	Y	Y	Y	9/14/2006	3/27/2008	8/11/2008	4/16/2008	Visit comp	6/16/2009	Y	Y	Family is pl	6/15/2012	6/15/2013
4			Y	Y	Y	Y	8/23/2006	3/17/2008	8/1/2008	9/18/2008	Visit comp	6/19/2009				6/18/2012	6/18/2013
4			Y	Y	Y	Y	8/22/2006	3/24/2008	8/8/2008	7/11/2008	Visit comp	6/23/2009				6/22/2012	6/22/2013
4			Y	Y	Y	Y	9/18/2006	4/5/2008	8/20/2008	4/14/2008	Visit comp	6/24/2009				6/23/2012	6/23/2013
18			Y	Y	Y	Y	8/21/2006	3/19/2008	8/3/2008	3/24/2008	Visit comp	6/26/2009				6/25/2012	6/25/2013
14			Y	Y	Y	Y	9/15/2006	4/3/2008	8/18/2008	4/2/2008	Visit comp	6/28/2009	Y	Y	Family is pl	6/27/2012	6/27/2013
16			Y	Y	Y	Y	10/11/2006	4/11/2008	8/26/2008	5/22/2008	Visit comp	6/29/2009				6/28/2012	6/28/2013
16			Y	Y	Y	Y	9/5/2006	3/27/2008	8/11/2008	3/28/2008	Visit comp	6/29/2009				6/28/2012	6/28/2013
16			Y	Y	Y	Y	9/22/2006	3/27/2008	8/11/2008	3/28/2008	Visit comp	6/29/2009				6/28/2012	6/28/2013
16			Y	Y	Y	Y	9/22/2006	3/27/2008	8/11/2008	3/28/2008	Visit comp	6/29/2009				6/28/2012	6/28/2013
19			Y	Y	Y	Y	11/7/2006	4/4/2008	8/19/2008	5/13/2008	Visit comp	6/29/2009				6/28/2012	6/28/2013
15			Y	Y	Y	Y	8/31/2006	4/1/2008	8/16/2008	7/9/2008	Visit comp	6/30/2009				6/29/2012	6/29/2013
14			Y	Y	Y	Y	9/20/2006	4/1/2008	8/16/2008	4/22/2008	Visit comp	7/4/2009	Y	Y	Family is pl	7/3/2012	7/3/2013
16			Y	Y	Y	Y	10/16/2006	4/23/2008	9/7/2008	5/6/2008	Visit comp	7/5/2009				7/4/2012	7/4/2013
16			Y	Y	Y	Y	9/21/2006	4/3/2008	8/18/2008	8/21/2008	Visit comp	7/10/2009				7/9/2012	7/9/2013
14			Y	Y	Y	Y	9/27/2006	4/19/2008	9/3/2008	6/3/2008	Visit comp	7/12/2009				7/11/2012	7/11/2013
18			Y	Y	Y	Y	10/8/2006	4/17/2008	9/1/2008	4/28/2008	Visit comp	7/24/2009				7/23/2012	7/23/2013
14			Y	Y	Y	Y	10/5/2006	4/27/2008	9/11/2008	6/17/2008	Visit comp	7/27/2009				7/26/2012	7/26/2013

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4		Y	Y	Y	Y	12/8/2006	5/21/2008	10/6/2008	5/23/2008	Visit comp	8/8/2009	8/7/2012	8/7/2013
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16		Y	Y	Y	Y	10/26/2006	5/15/2008	9/30/2008	5/5/2008	Visit comp	8/12/2009	8/11/2012	8/11/2013
18		Y	Y	Y	Y	11/12/2006	5/28/2008	10/13/2008	6/30/2008	Visit comp	8/13/2009	8/12/2012	8/12/2013
16		Y	Y	Y	Y	9/22/2006	5/25/2008	10/10/2008	8/14/2008	Visit comp	8/14/2009	8/13/2012	8/13/2013
19		Y	Y	Y	Y	1/4/2007	5/30/2008	10/15/2008	5/20/2008	Visit comp	8/16/2009	8/15/2012	8/15/2013
4		Y	Y	Y	Y	11/29/2006	6/2/2008	10/17/2008	9/22/2008	Visit comp	8/23/2009	8/22/2012	8/22/2013
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18		Y	Y	Y	Y	11/17/2006	5/29/2008	10/14/2008	6/2/2008	Visit comp	8/27/2009	8/26/2012	8/26/2013
14		Y	Y	Y	Y	11/17/2006	6/8/2008	10/23/2008	7/23/2008	Visit comp	9/5/2009	9/4/2012	9/4/2013
4		Y	Y	Y	Y	12/1/2006	6/12/2008	10/27/2008	6/18/2008	Visit comp	9/6/2009	9/5/2012	9/5/2013
3		Y	Y	Y	Y	11/28/2006	6/6/2008	10/21/2008	7/17/2008	Visit comp	9/7/2009	9/6/2012	9/6/2013
25		Y	Y	Y	Y	12/22/2006	6/14/2008	10/29/2008	11/12/2008	Visit comp	9/9/2009	9/8/2012	9/8/2013
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15		Y	Y	Y	Y	12/28/2006	6/17/2008	11/1/2008	8/26/2008	Visit comp	9/21/2009	9/20/2012	9/20/2013
25		Y	Y	Y	Y	12/7/2006	6/18/2008	11/2/2008			9/23/2009	9/22/2012	9/22/2013
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25		Y	Y	Y	Y	1/4/2007	7/15/2008	11/30/2008	11/19/2008	Visit comp	9/28/2009	9/27/2012	9/27/2013
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25		Y	Y	Y	Y	12/7/2006	6/26/2008	11/10/2008		Lost to folu	10/3/2009	10/2/2012	10/2/2013
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16		Y	Y	Y	Y	1/16/2007	7/22/2008	12/7/2008	7/24/2008	Visit comp	10/10/2009	10/9/2012	10/9/2013
15		Y	Y	N	Y	12/13/2006	7/13/2008	11/28/2008	7/23/2008	Visit comp	10/21/2009	10/20/2012	10/20/2013
25		Y	Y	Y	Y	1/5/2007	7/28/2008	12/13/2008	1/21/2009	Visit comp	10/27/2009	10/26/2012	10/26/2013
18		Y	Y	Y	Y	12/23/2006	7/22/2008	12/7/2008	8/13/2008	Visit comp	10/29/2009	10/28/2012	10/28/2013
18		Y	Y	Y	Y	12/27/2006	7/22/2008	12/7/2008	8/13/2008	Visit comp	10/29/2009	10/28/2012	10/28/2013
18		Y	Y	Y	Y	12/25/2006	7/22/2008	12/7/2008	8/13/2008	Visit comp	10/29/2009	10/28/2012	10/28/2013
4		Y	Y	Y	Y	2/19/2007	8/5/2008	12/20/2008	10/31/2008	Visit comp	10/30/2009	10/29/2012	10/29/2013
16		Y	Y	Y	Y	1/19/2007	7/28/2008	12/13/2008	8/1/2008	Visit comp	11/2/2009	11/1/2012	11/1/2013
16		Y	Y	Y	Y	2/7/2007	8/18/2008	1/2/2009	8/22/2008	Visit comp	11/3/2009	11/2/2012	11/2/2013
18		Y	Y	Y	Y	2/8/2007	8/19/2008	1/3/2009	8/25/2008	Visit comp	11/4/2009	11/3/2012	11/3/2013
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16		Y	Y	Y	Y	1/17/2007	8/2/2008	12/17/2008	9/4/2008	Visit comp	11/7/2009	11/6/2012	11/6/2013
18		Y	Y	Y	Y	2/4/2007	8/2/2008	12/17/2008	8/6/2008	Visit comp	11/7/2009	11/6/2012	11/6/2013
15		Y	Y	Y	Y	2/13/2007	8/16/2008	12/31/2008	10/22/2008	Visit comp	11/8/2009	11/7/2012	11/7/2013
16		Y	Y	Y	Y	1/15/2007	8/13/2008	12/28/2008	8/14/2008	Visit comp	11/12/2009	11/11/2012	11/11/2013
16		Y	Y	Y	Y	1/19/2007	8/15/2008	12/30/2008	8/15/2008	Visit comp	11/13/2009	11/12/2012	11/12/2013
25		Y	Y	Y	Y	1/22/2007	8/9/2008	12/24/2008		Lost to folu	11/15/2009	11/14/2012	11/14/2013
16		Y	Y	Y	Y	2/28/2007	8/29/2008	1/13/2009	12/4/2008	Visit comp	11/17/2009	11/16/2012	11/16/2013
16		Y	Y	Y	Y	1/16/2007	8/12/2008	12/27/2008		Lost to folu	11/19/2009	11/18/2012	11/18/2013
16		Y	Y	Y	Y	2/16/2007	8/29/2008	1/13/2009	9/19/2008	Visit comp	11/22/2009	11/21/2012	11/21/2013
16		Y	Y	Y	Y	2/20/2007	8/29/2008	1/13/2009	9/19/2008	Visit comp	11/22/2009	11/21/2012	11/21/2013
16		Y	Y	Y	Y	3/2/2007	8/29/2008	1/13/2009	9/19/2008		11/22/2009	11/21/2012	11/21/2013
23		Y	Y	Y	Y	2/5/2007	8/16/2008	12/31/2008	11/6/2008	Visit comp	11/23/2009	11/22/2012	11/22/2013

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16	(b) (6)	Y	Y	Y	Y	2/20/2007	8/21/2008	1/5/2009	10/9/2008	Visit comp	11/25/2009	11/24/2012	11/24/2013
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3		Y	Y	Y	Y	2/19/2007	9/9/2008	1/24/2009	9/9/2008	Visit comp	12/5/2009	12/4/2012	12/4/2013
14		Y	Y	Y	Y	2/9/2007	9/3/2008	1/18/2009	10/29/2008	Visit comp	12/6/2009	12/5/2012	12/5/2013
4		Y	Y	Y	Y	2/27/2007	9/15/2008	1/30/2009	10/28/2008	Visit comp	12/7/2009	12/6/2012	12/6/2013
23		Y	Y	Y	Y	2/23/2007	9/26/2008	2/10/2009	10/21/2008	Visit comp	12/8/2009	12/7/2012	12/7/2013
24		Y	Y	Y	Y	3/21/2007	9/24/2008	2/8/2009	12/30/2008	Visit comp	12/8/2009	12/7/2012	12/7/2013
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18		Y	Y	Y	Y	3/10/2007	9/17/2008	2/1/2009	1/13/2009	Visit comp	12/15/2009	12/14/2012	12/14/2013
23		Y	Y	Y	Y	3/1/2007	9/19/2008	2/3/2009	9/30/2008	Visit comp	12/17/2009	12/16/2012	12/16/2013
3		Y	Y	Y	Y	2/22/2007	9/21/2008	2/5/2009	10/14/2008	Visit comp	12/23/2009	12/22/2012	12/22/2013
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3		Y	Y	Y	Y	3/7/2007	9/19/2008	2/3/2009	12/2/2008	Visit comp	12/27/2009	12/26/2012	12/26/2013
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23		Y	Y	Y	Y	4/9/2007	9/23/2008	2/7/2009	10/21/2008	Visit comp	12/31/2009	12/30/2012	12/30/2013
4		Y	Y	Y	Y	2/28/2007	9/29/2008	2/13/2009	1/30/2009	Visit comp	1/1/2010	12/31/2012	12/31/2013
24		Y	Y	Y	Y	4/25/2007	10/11/2008	2/26/2009	12/29/2008	Visit comp	1/1/2010	12/31/2012	12/31/2013
4		Y	Y	Y	Y	2/27/2007	10/1/2008	2/16/2009	10/31/2008	Visit comp	1/2/2010	1/1/2013	1/1/2014
14		Y	Y	Y	Y	5/8/2007	10/25/2008	3/12/2009	1/21/2009	Visit comp	1/6/2010	1/5/2013	1/5/2014
15		Y	Y	Y	Y	4/3/2007	10/15/2008	3/2/2009	11/17/2008	Visit comp	1/7/2010	1/6/2013	1/6/2014
16		Y	Y	Y	Y	4/12/2007	10/17/2008	3/4/2009	10/31/2008	Visit comp	1/7/2010	1/6/2013	1/6/2014
4		Y	Y	Y	Y	4/20/2007	10/15/2008	3/2/2009	10/20/2008	Visit comp	1/11/2010	1/10/2013	1/10/2014
24		Y	Y	Y	Y	3/21/2007	10/5/2008	2/20/2009	12/15/2008	Visit comp	1/11/2010	1/10/2013	1/10/2014
3		Y	Y	N	Y	3/13/2007	10/11/2008	2/26/2009	3/12/2009	Visit comp	1/13/2010	1/12/2013	1/12/2014
5		Y	Y	Y	Y	4/29/2007	10/24/2008	3/11/2009		Died after c	1/17/2010	1/16/2013	1/16/2014
12		Y	Y	Y	Y	5/18/2007	10/21/2008	3/8/2009	11/7/2008		1/23/2010	1/22/2013	1/22/2014
16		Y	Y	Y	Y	4/5/2007	10/20/2008	3/7/2009	11/13/2008	Visit comp	1/26/2010	1/25/2013	1/25/2014
16		Y	Y	Y	Y	4/5/2007	10/20/2008	3/7/2009	11/13/2008	Visit comp	1/26/2010	1/25/2013	1/25/2014
16		Y	Y	Y	Y	3/29/2007	10/20/2008	3/7/2009	11/13/2008	Visit comp	1/26/2010	1/25/2013	1/25/2014
16		Y	Y	Y	Y	5/3/2007	10/24/2008	3/11/2009		Died after c	1/28/2010	1/27/2013	1/27/2014
19		Y	Y	Y	Y	5/14/2007	11/13/2008	3/28/2009	9/25/2008	Visit comp	1/31/2010	1/30/2013	1/30/2014
4		Y	Y	Y	Y	6/4/2007	11/16/2008	3/31/2009	1/12/2009	Visit comp	2/2/2010	2/1/2013	2/1/2014
18		Y	Y	Y	Y	4/17/2007	10/27/2008	3/14/2009			2/2/2010	2/1/2013	2/1/2014
15		Y	Y	Y	Y	6/7/2007	11/4/2008	3/19/2009	12/17/2008	Visit comp	2/5/2010	2/4/2013	2/4/2014
15		Y	Y	Y	Y	5/7/2007	11/4/2008	3/19/2009	12/10/2008	Visit comp	2/5/2010	2/4/2013	2/4/2014
3		Y	Y	Y	Y	5/16/2007	11/17/2008	4/1/2009	11/25/2008	Visit comp	2/9/2010	2/8/2013	2/8/2014
26		Y	Y	Y	Y	4/28/2007	11/12/2008	3/27/2009	3/24/2009		2/9/2010	2/8/2013	2/8/2014
14		Y	Y	Y	Y	5/2/2007	11/13/2008	3/28/2009	12/9/2008	Visit comp	2/10/2010	2/9/2013	2/9/2014
14		Y	Y	Y	Y	5/2/2007	11/20/2008	4/4/2009	2/24/2009	Visit comp	2/12/2010	2/11/2013	2/11/2014
23		Y	Y	Y	Y	5/30/2007	11/16/2008	3/31/2009	12/23/2008	Visit comp	2/12/2010	2/11/2013	2/11/2014
16		Y	Y	Y	Y	4/24/2007	11/19/2008	4/3/2009	4/11/2009	Visit comp	2/17/2010	2/16/2013	2/16/2014
15		Y	Y	Y	Y	4/16/2007	11/11/2008	3/26/2009	11/19/2008	Visit comp	2/18/2010	2/17/2013	2/17/2014
4		Y	Y	Y	Y	6/1/2007	12/7/2008	4/22/2009	2/24/2009	Visit comp	2/28/2010	2/27/2013	2/27/2014
14		Y	Y	Y	Y	6/4/2007	12/15/2008	4/30/2009	12/3/2008	Visit comp	2/28/2010	2/27/2013	2/27/2014
4		Y	Y	Y	Y	6/15/2007	12/7/2008	4/22/2009	2/6/2009	Visit comp	3/1/2010	2/28/2013	2/28/2014
23		Y	Y	Y	Y	4/27/2007	11/25/2008	4/9/2009	12/18/2008	Visit comp	3/1/2010	2/28/2013	2/28/2014
23		Y	Y	Y	Y	6/19/2007	12/5/2008	4/20/2009	2/19/2009	Visit comp	3/1/2010	2/28/2013	2/28/2014
23		Y	Y	Y	Y	5/30/2007	12/5/2008	4/20/2009	2/19/2009	Visit comp	3/1/2010	2/28/2013	2/28/2014

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14	[redacted]	Y	Y	Y	Y	5/8/2007	11/29/2008	4/13/2009	1/13/2009	Visit comp	3/2/2010	3/1/2013 3/1/2014
16		Y	Y	Y	Y	5/4/2007	11/30/2008	4/14/2009	1/9/2009	Visit comp	3/2/2010	3/1/2013 3/1/2014
3		Y	Y	Y	Y	6/15/2007	12/15/2008	4/30/2009	1/6/2009	Visit comp	3/4/2010	3/3/2013 3/3/2014
5		Y	Y	Y	Y	6/26/2007	12/23/2008	5/8/2009	1/29/2009	Visit comp	3/7/2010	3/6/2013 3/6/2014
23		Y	Y	Y	Y	5/16/2007	12/1/2008	4/16/2009	12/11/2008	Visit comp	3/9/2010	3/8/2013 3/8/2014
14		Y	Y	Y	Y	6/11/2007	12/27/2008	5/12/2009	3/10/2009	Visit comp	3/10/2010	3/9/2013 3/9/2014
16		Y	Y	Y	Y	5/22/2007	12/6/2008	4/21/2009	2/20/2009	Visit comp	3/10/2010	3/9/2013 3/9/2014
5		Y	Y	Y	Y	5/23/2007	12/7/2008	4/22/2009	4/22/2009	Visit comp	3/12/2010	3/11/2013 3/11/2014
14		Y	Y	Y	Y	6/5/2007	12/19/2008	5/4/2009	2/17/2009	Visit comp	3/13/2010	3/12/2013 3/12/2014
16		Y	Y	Y	Y	6/28/2007	12/29/2008	5/14/2009	2/6/2009	Visit comp	3/13/2010	3/12/2013 3/12/2014
22		Y	Y	Y	Y	6/7/2007	12/12/2008	4/27/2009	1/21/2009	Visit comp	3/15/2010	3/14/2013 3/14/2014
3		Y	Y	Y	Y	5/15/2007	12/15/2008	4/30/2009	1/27/2009	Visit comp	3/18/2010	3/17/2013 3/17/2014
18		Y	Y	Y	Y	7/21/2007	12/29/2008	5/14/2009	2/12/2009	Visit comp	3/22/2010	3/21/2013 3/21/2014
22		Y	Y	Y	Y	6/8/2007	12/27/2008	5/12/2009	1/15/2009	Visit comp	3/23/2010	3/22/2013 3/22/2014
16		Y	Y	Y	Y	5/30/2007	12/26/2008	5/11/2009		Died after c	3/26/2010	3/25/2013 3/25/2014
14		Y	Y	Y	Y	6/5/2007	1/1/2009	5/16/2009	1/14/2009	Visit comp	3/28/2010	3/27/2013 3/27/2014
23		Y	Y	Y	Y	5/23/2007	12/24/2008	5/9/2009	1/27/2009	Visit comp	3/28/2010	3/27/2013 3/27/2014
14		Y	Y	Y	Y	7/10/2007	1/15/2009	5/30/2009	1/27/2009	Visit comp	4/1/2010	3/31/2013 3/31/2014
14		Y	Y	Y	Y	6/22/2007	1/12/2009	5/27/2009	2/3/2009	Visit comp	4/3/2010	4/2/2013 4/2/2014
14		Y	Y	Y	Y	6/20/2007	1/4/2009	5/19/2009	12/17/2008	Visit comp	4/5/2010	4/4/2013 4/4/2014
14		Y	Y	Y	Y	7/19/2007	1/21/2009	6/5/2009	3/24/2009	Visit comp	4/6/2010	4/5/2013 4/5/2014
26		Y	Y	Y	Y	6/28/2007	1/4/2009	5/19/2009	3/30/2009	Visit comp	4/7/2010	4/6/2013 4/6/2014
3		Y	Y	Y	Y	5/15/2007	1/3/2009	5/18/2009	4/9/2009	Visit comp	4/8/2010	4/7/2013 4/7/2014
15		Y	Y	Y	Y	7/3/2007	1/6/2009	5/21/2009		Died after c	4/8/2010	4/7/2013 4/7/2014
24		Y	Y	Y	Y	6/25/2007	1/1/2009	5/16/2009	4/1/2009	Visit comp	4/10/2010	4/9/2013 4/9/2014
4		Y	Y	Y	Y	7/3/2007	1/26/2009	6/10/2009	2/10/2009	Visit comp	4/25/2010	4/24/2013 4/24/2014
16		Y	Y	Y	Y	6/29/2007	2/5/2009	6/20/2009			4/28/2010	4/27/2013 4/27/2014
16		Y	Y	Y	Y	6/29/2007	1/23/2009	6/7/2009	2/13/2009	Visit comp	4/29/2010	4/28/2013 4/28/2014
4		Y	Y	Y	Y	7/12/2007	1/21/2009	6/5/2009	1/21/2009	Visit comp	4/30/2010	4/29/2013 4/29/2014
4		Y	Y	Y	Y	7/13/2007	1/21/2009	6/5/2009	1/21/2009	Visit comp	4/30/2010	4/29/2013 4/29/2014
5		Y	Y	Y	Y	8/27/2007	2/6/2009	6/21/2009		Died after c	5/1/2010	4/30/2013 4/30/2014
16		Y	Y	Y	Y	7/5/2007	1/27/2009	6/11/2009			5/3/2010	5/2/2013 5/2/2014
18		Y	Y	Y	Y	8/13/2007	2/18/2009	7/3/2009			5/4/2010	5/3/2013 5/3/2014
12		Y	Y	Y	Y	8/15/2007	2/20/2009	7/5/2009	3/10/2009	Visit comp	5/8/2010	5/7/2013 5/7/2014
15		Y	Y	Y	Y	7/13/2007	2/4/2009	6/19/2009	4/8/2009	Visit comp	5/8/2010	5/7/2013 5/7/2014
23		Y	Y	Y	Y	7/4/2007	2/4/2009	6/19/2009	4/7/2009	Visit comp	5/11/2010	5/10/2013 5/10/2014
23		Y	Y	Y	Y	8/3/2007	2/8/2009	6/23/2009	2/17/2009	Visit comp	5/11/2010	5/10/2013 5/10/2014
23		Y	Y	Y	Y	9/6/2007	2/19/2009	7/4/2009		Another Ce	5/12/2010	5/11/2013 5/11/2014
25		Y	Y	Y	Y	8/24/2007	2/26/2009	7/11/2009	4/9/2009	Visit comp	5/13/2010	5/12/2013 5/12/2014
14		Y	Y	Y	Y	7/19/2007	2/19/2009	7/4/2009	4/15/2009	Visit comp	5/21/2010	5/20/2013 5/20/2014
25		Y	Y	Y	Y	8/6/2007	2/22/2009	7/7/2009	5/4/2009	Visit comp	5/22/2010	5/21/2013 5/21/2014
4		Y	Y	Y	Y	7/31/2007	2/24/2009	7/9/2009	3/24/2009	Visit comp	5/23/2010	5/22/2013 5/22/2014
16		Y	Y	Y	Y	8/7/2007	2/18/2009	7/3/2009	3/5/2009	Visit comp	5/25/2010	5/24/2013 5/24/2014
16		Y	Y	Y	Y	8/13/2007	2/22/2009	7/7/2009	4/30/2009	Visit comp	5/26/2010	5/25/2013 5/25/2014
16		Y	Y	Y	Y	7/27/2007	2/20/2009	7/5/2009	5/28/2009	Visit comp	5/26/2010	5/25/2013 5/25/2014
16		Y	Y	Y	Y	7/30/2007	2/20/2009	7/5/2009	5/28/2009	Visit comp	5/26/2010	5/25/2013 5/25/2014
19		Y	Y	Y	Y	9/14/2007	3/7/2009	7/22/2009	3/31/2009	Visit comp	5/28/2010	5/27/2013 5/27/2014
4		Y	Y	Y	Y	8/7/2007	2/26/2009	7/11/2009			5/29/2010	5/28/2013 5/28/2014
24		Y	Y	Y	Y	8/23/2007	3/7/2009	7/22/2009			6/2/2010	6/1/2013 6/1/2014
23		Y	Y	Y	Y	9/6/2007	3/17/2009	8/1/2009	4/7/2009	Visit comp	6/10/2010	6/9/2013 6/9/2014
3		Y	Y	Y	Y	8/20/2007	3/14/2009	7/29/2009	3/17/2009	Visit comp	6/12/2010	6/11/2013 6/11/2014
3		Y	Y	Y	Y	8/8/2007	3/7/2009	7/22/2009			6/14/2010	6/13/2013 6/13/2014
3		Y	Y	Y	Y	10/15/2007	3/28/2009	8/12/2009			6/15/2010	6/14/2013 6/14/2014
23		Y	Y	Y	Y	8/7/2007	3/9/2009	7/24/2009	3/17/2009	Visit comp	6/16/2010	6/15/2013 6/15/2014

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23	(b) (6)	Y	Y	Y	Y	9/20/2007	3/9/2009	7/24/2009	3/26/2009	Visit comp	6/16/2010	6/15/2013	6/15/2014
23		Y	Y	Y	Y	9/20/2007	3/9/2009	7/24/2009	3/26/2009		6/16/2010	6/15/2013	6/15/2014
23		Y	Y	Y	Y	9/26/2007	3/9/2009	7/24/2009	3/31/2009	Visit comp	6/16/2010	6/15/2013	6/15/2014
3		Y	Y	Y	Y	8/24/2007	3/14/2009	7/29/2009	3/17/2009	Visit comp	6/19/2010	6/18/2013	6/18/2014
23		Y	Y	Y	Y	9/4/2007	3/22/2009	8/6/2009			6/24/2010	6/23/2013	6/23/2014
4		Y	Y	Y	Y	9/20/2007	4/2/2009	8/17/2009	4/16/2009	Visit comp	6/25/2010	6/24/2013	6/24/2014
5		Y	Y	Y	Y	10/23/2007	4/12/2009	8/27/2009			6/25/2010	6/24/2013	6/24/2014
5		Y	Y	Y	Y	9/18/2007	3/28/2009	8/12/2009			6/26/2010	6/25/2013	6/25/2014
15		Y	Y	Y	Y	9/12/2007	4/2/2009	8/17/2009	5/4/2009	Visit comp	6/27/2010	6/26/2013	6/26/2014
18		Y	Y	Y	Y	9/20/2007	3/22/2009	8/6/2009			6/28/2010	6/27/2013	6/27/2014
23		Y	Y	Y	Y	10/12/2007	3/30/2009	8/14/2009	4/2/2009	Visit comp	6/29/2010	6/28/2013	6/28/2014
5		Y	Y	Y	Y	10/30/2007	4/16/2009	8/31/2009	4/30/2009	Visit comp	7/2/2010	7/1/2013	7/1/2014
19		Y	Y	Y	Y	10/23/2007	4/6/2009	8/21/2009		Died after c	7/6/2010	7/5/2013	7/5/2014
25		Y	Y	Y	Y	9/6/2007	3/29/2009	8/13/2009	5/4/2009	Visit comp	7/6/2010	7/5/2013	7/5/2014
4		Y	Y	Y	Y	9/11/2007	4/6/2009	8/21/2009	4/23/2009	Visit comp	7/7/2010	7/6/2013	7/6/2014
23		Y	Y	Y	Y	10/4/2007	4/18/2009	9/2/2009			7/7/2010	7/6/2013	7/6/2014
23		Y	Y	Y	Y	9/7/2007	4/1/2009	8/16/2009	5/5/2009	Visit comp	7/8/2010	7/7/2013	7/7/2014
22		Y	Y	Y	Y	10/3/2007	4/14/2009	8/29/2009			7/9/2010	7/8/2013	7/8/2014
25		Y	Y	N	Y	10/20/2007	4/4/2009	8/19/2009	4/28/2009	Visit comp	7/9/2010	7/8/2013	7/8/2014
23		Y	Y	Y	Y	11/3/2007	4/16/2009	8/31/2009	4/14/2009	Visit comp	7/13/2010	7/12/2013	7/12/2014
3		Y	Y	Y	Y	9/6/2007	4/19/2009	9/3/2009			7/19/2010	7/18/2013	7/18/2014
18		Y	Y	Y	Y	10/23/2007	5/4/2009	9/19/2009			7/21/2010	7/20/2013	7/20/2014
3		Y	Y	Y	Y	10/25/2007	4/30/2009	9/14/2009			7/22/2010	7/21/2013	7/21/2014
16		Y	Y	Y	Y	10/22/2007	5/8/2009	9/23/2009			7/23/2010	7/22/2013	7/22/2014
3		Y	Y	Y	Y	9/25/2007	4/19/2009	9/3/2009	4/28/2009	Visit comp	7/24/2010	7/23/2013	7/23/2014
3		Y	Y	Y	Y	9/25/2007	4/19/2009	9/3/2009	4/28/2009	Visit comp	7/24/2010	7/23/2013	7/23/2014
16		Y	Y	Y	Y	10/1/2007	5/3/2009	9/18/2009			7/25/2010	7/24/2013	7/24/2014
23		Y	Y	Y	Y	11/15/2007	5/6/2009	9/21/2009	5/14/2009	Visit comp	7/29/2010	7/28/2013	7/28/2014
23		Y	Y	Y	Y	11/2/2007	5/6/2009	9/21/2009	5/14/2009	Visit comp	7/29/2010	7/28/2013	7/28/2014
14		Y	Y	Y	Y	10/3/2007	5/2/2009	9/17/2009			8/2/2010	8/1/2013	8/1/2014
25		Y	Y	Y	Y	11/1/2007	5/20/2009	10/5/2009			8/4/2010	8/3/2013	8/3/2014
12		Y	Y	Y	Y	11/7/2007	5/21/2009	10/6/2009			8/8/2010	8/7/2013	8/7/2014
26		Y	Y	Y	Y	11/14/2007	5/16/2009	10/1/2009		Died after c	8/8/2010	8/7/2013	8/7/2014
25		Y	Y	Y	Y	10/19/2007	5/10/2009	9/25/2009			8/9/2010	8/8/2013	8/8/2014
14		Y	Y	Y	Y	10/30/2007	5/26/2009	10/11/2009			8/13/2010	8/12/2013	8/12/2014
23		Y	Y	Y	Y	10/30/2007	5/24/2009	10/9/2009			8/13/2010	8/12/2013	8/12/2014
15		Y	Y	Y	Y	11/2/2007	5/29/2009	10/14/2009			8/14/2010	8/13/2013	8/13/2014
25		Y	Y	Y	Y	11/20/2007	5/14/2009	9/29/2009			8/14/2010	8/13/2013	8/13/2014
25		Y	Y	Y	Y	10/19/2007	5/8/2009	9/23/2009	5/26/2009	Visit comp	8/14/2010	8/13/2013	8/13/2014
3		Y	Y	Y	Y	10/26/2007	5/20/2009	10/5/2009			8/16/2010	8/15/2013	8/15/2014
14		Y	Y	Y	Y	10/12/2007	5/9/2009	9/24/2009			8/16/2010	8/15/2013	8/15/2014
14		Y	Y	Y	Y	11/9/2007	6/3/2009	10/18/2009			8/23/2010	8/22/2013	8/22/2014
12		Y	Y	Y	Y	12/24/2007	6/12/2009	10/27/2009			8/24/2010	8/23/2013	8/23/2014
16		Y	Y	Y	Y	12/7/2007	5/30/2009	10/15/2009			8/31/2010	8/30/2013	8/30/2014
14		Y	Y	Y	Y	11/9/2007	6/8/2009	10/23/2009			9/1/2010	8/31/2013	8/31/2014
15		Y	Y	Y	Y	11/25/2007	5/30/2009	10/15/2009			9/3/2010	9/2/2013	9/2/2014
23		Y	Y	Y	Y	12/13/2007	6/10/2009	10/25/2009			9/3/2010	9/2/2013	9/2/2014
16		Y	Y	Y	Y	12/4/2007	6/12/2009	10/27/2009			9/4/2010	9/3/2013	9/3/2014
25		Y	Y	Y	Y	11/15/2007	6/8/2009	10/23/2009			9/4/2010	9/3/2013	9/3/2014
25		Y	Y	Y	Y	11/15/2007	6/8/2009	10/23/2009			9/4/2010	9/3/2013	9/3/2014
16		Y	Y	Y	Y	12/18/2007	6/12/2009	10/27/2009			9/5/2010	9/4/2013	9/4/2014
15		Y	Y	Y	Y	12/4/2007	6/8/2009	10/23/2009			9/13/2010	9/12/2013	9/12/2014
25		Y	Y	Y	Y	11/26/2007	6/20/2009	11/4/2009			9/16/2010	9/15/2013	9/15/2014
3		Y	Y	Y	Y	1/16/2008	6/27/2009	11/11/2009			9/19/2010	9/18/2013	9/18/2014

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16	(b) (6)	Y	Y	Y	Y	11/20/2007	6/25/2009	11/9/2009		9/19/2010	9/18/2013	9/18/2014
15		Y	Y	Y	Y	12/27/2007	7/10/2009	11/25/2009		9/20/2010	9/19/2013	9/19/2014
18		Y	Y	Y	Y	12/4/2007	6/17/2009	11/1/2009		9/20/2010	9/19/2013	9/19/2014
14		Y	Y	Y	Y	12/5/2007	6/28/2009	11/12/2009		9/24/2010	9/23/2013	9/23/2014
14		Y	Y	Y	Y	12/6/2007	6/28/2009	11/12/2009		9/24/2010	9/23/2013	9/23/2014
18		Y	Y	Y	Y	12/6/2007	6/21/2009	11/5/2009		9/25/2010	9/24/2013	9/24/2014
19		Y	Y	Y	Y	12/6/2007	6/23/2009	11/7/2009		9/25/2010	9/24/2013	9/24/2014
15		Y	Y	Y	Y	11/29/2007	7/2/2009	11/17/2009		9/26/2010	9/25/2013	9/25/2014
15		Y	Y	N	Y	11/18/2007	6/19/2009	11/3/2009		9/26/2010	9/25/2013	9/25/2014
14		Y	Y	Y	Y	12/12/2007	7/5/2009	11/20/2009		9/28/2010	9/27/2013	9/27/2014
19		Y	Y	Y	Y	1/16/2008	6/29/2009	11/13/2009		9/30/2010	9/29/2013	9/29/2014
22		Y	Y	Y	Y	12/28/2007	7/6/2009	11/21/2009		9/30/2010	9/29/2013	9/29/2014
16		Y	Y	Y	Y	1/28/2008	7/15/2009	11/30/2009		10/3/2010	10/2/2013	10/2/2014
16		Y	Y	Y	Y	12/31/2007	7/13/2009	11/28/2009		10/4/2010	10/3/2013	10/3/2014
12		Y	Y	Y	Y	1/7/2008	7/9/2009	11/24/2009		10/9/2010	10/8/2013	10/8/2014
3		Y	Y	Y	Y	12/14/2007	7/7/2009	11/22/2009		10/10/2010	10/9/2013	10/9/2014
4		Y	Y	Y	Y	1/28/2008	7/7/2009	11/22/2009		10/12/2010	10/11/2013	10/11/2014
3		Y	Y	Y	Y	2/11/2008	7/26/2009	12/11/2009		10/13/2010	10/12/2013	10/12/2014
25		Y	Y	Y	Y	1/31/2008	7/31/2009	12/15/2009	Lost to folu	10/23/2010	10/22/2013	10/22/2014
3		Y	Y	Y	Y	2/7/2008	8/2/2009	12/17/2009		10/25/2010	10/24/2013	10/24/2014
19		Y	Y	Y	Y	1/30/2008	8/13/2009	12/28/2009		10/26/2010	10/25/2013	10/25/2014
19		Y	Y	Y	Y	1/30/2008	8/13/2009	12/28/2009		10/26/2010	10/25/2013	10/25/2014
16		Y	Y	Y	Y	12/12/2007	7/21/2009	12/6/2009		10/27/2010	10/26/2013	10/26/2014
3		Y	Y	Y	Y	2/20/2008	8/12/2009	12/27/2009		11/1/2010	10/31/2013	10/31/2014
14		Y	Y	Y	Y	12/31/2007	7/30/2009	12/15/2009		11/6/2010	11/5/2013	11/5/2014
15		Y	Y	Y	Y	1/20/2008	8/18/2009	1/2/2010		11/7/2010	11/6/2013	11/6/2014
22		Y	Y	Y	Y	2/11/2008	8/22/2009	1/6/2010		11/9/2010	11/8/2013	11/8/2014
16		Y	Y	Y	Y	2/12/2008	8/17/2009	1/1/2010		11/10/2010	11/9/2013	11/9/2014
16		Y	Y	Y	Y	1/14/2008	8/4/2009	12/19/2009		11/11/2010	11/10/2013	11/10/2014
16		Y	Y	Y	Y	1/25/2008	8/8/2009	12/23/2009		11/13/2010	11/12/2013	11/12/2014
12		Y	Y	Y	Y	1/31/2008	8/18/2009	1/2/2010		11/15/2010	11/14/2013	11/14/2014
16		Y	Y	Y	Y	1/21/2008	8/18/2009	1/2/2010		11/15/2010	11/14/2013	11/14/2014
16		Y	Y	Y	Y	2/11/2008	9/2/2009	1/17/2010		11/20/2010	11/19/2013	11/19/2014
18		Y	Y	Y	Y	2/27/2008	9/4/2009	1/19/2010		11/21/2010	11/20/2013	11/20/2014
4		Y	Y	Y	Y	3/10/2008	8/16/2009	12/31/2009		11/22/2010	11/21/2013	11/21/2014
3		Y	Y	Y	Y	2/14/2008	8/17/2009	1/1/2010		11/24/2010	11/23/2013	11/23/2014
18		Y	Y	Y	Y	3/3/2008	9/4/2009	1/19/2010		11/25/2010	11/24/2013	11/24/2014
24		Y	Y	Y	Y	2/7/2008	8/29/2009	1/13/2010		11/25/2010	11/24/2013	11/24/2014
25		Y	Y	Y	Y	2/7/2008	8/18/2009	1/2/2010		11/25/2010	11/24/2013	11/24/2014
3		Y	Y	Y	Y	1/31/2008	8/27/2009	1/11/2010		11/29/2010	11/28/2013	11/28/2014
24		Y	Y	Y	Y	2/19/2008	9/10/2009	1/25/2010		12/2/2010	12/1/2013	12/1/2014
18		Y	Y	Y	Y	3/12/2008	9/14/2009	1/29/2010		12/3/2010	12/2/2013	12/2/2014
15		Y	Y	Y	Y	1/25/2008	8/29/2009	1/13/2010		12/4/2010	12/3/2013	12/3/2014
23		Y	Y	Y	Y	2/11/2008	9/12/2009	1/27/2010		12/4/2010	12/3/2013	12/3/2014
14		Y	Y	Y	Y	2/13/2008	9/12/2009	1/27/2010		12/6/2010	12/5/2013	12/5/2014
14		Y	Y	Y	Y	2/15/2008	9/17/2009	2/1/2010		12/6/2010	12/5/2013	12/5/2014
16		Y	Y	Y	Y	3/11/2008	9/28/2009	2/12/2010		12/15/2010	12/14/2013	12/14/2014
3		Y	Y	Y	Y	4/7/2008	9/28/2009	2/12/2010		12/17/2010	12/16/2013	12/16/2014
18		Y	Y	Y	Y	3/12/2008	9/20/2009	2/4/2010		12/21/2010	12/20/2013	12/20/2014
16		Y	Y	Y	Y	3/10/2008	10/4/2009	2/19/2010		12/26/2010	12/25/2013	12/25/2014
5		Y	Y	Y	Y	2/22/2008	9/25/2009	2/9/2010		12/28/2010	12/27/2013	12/27/2014
16		Y	Y	Y	Y	3/13/2008	10/6/2009	2/21/2010		12/29/2010	12/28/2013	12/28/2014
3		Y	Y	Y	Y	4/21/2008	10/10/2009	2/25/2010		1/2/2011	1/1/2014	1/1/2015
16		Y	Y	Y	Y	2/25/2008	9/25/2009	2/9/2010		1/2/2011	1/1/2014	1/1/2015

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12	[redacted]	Y	Y	Y	3/24/2008	10/9/2009	2/24/2010		1/7/2011	1/6/2014	1/6/2015
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14		Y	Y	Y	3/12/2008	10/11/2009	2/26/2010		1/9/2011	1/8/2014	1/8/2015
16		Y	Y	Y	4/22/2008	10/21/2009	3/8/2010		1/9/2011	1/8/2014	1/8/2015
16		Y	Y	Y	3/17/2008	10/20/2009	3/7/2010		1/11/2011	1/10/2014	1/10/2015
16		Y	Y	Y	3/26/2008	10/5/2009	2/20/2010		1/12/2011	1/11/2014	1/11/2015
16		Y	Y	Y	4/8/2008	10/17/2009	3/4/2010		1/14/2011	1/13/2014	1/13/2015
26		Y	Y	Y	3/12/2008	10/11/2009	2/26/2010		1/15/2011	1/14/2014	1/14/2015
16		Y	Y	Y	5/7/2008	11/15/2009	3/30/2010		1/20/2011	1/19/2014	1/19/2015
16		Y	Y	Y	5/13/2008	10/29/2009	3/15/2010	Died after c	1/20/2011	1/19/2014	1/19/2015
14		Y	Y	Y	4/25/2008	10/16/2009	3/3/2010		1/23/2011	1/22/2014	1/22/2015
14		Y	Y	Y	5/14/2008	11/11/2009	3/26/2010		1/23/2011	1/22/2014	1/22/2015
14		Y	Y	Y	4/18/2008	11/6/2009	3/21/2010		1/29/2011	1/28/2014	1/28/2015
16		Y	Y	Y	4/2/2008	11/3/2009	3/18/2010		1/29/2011	1/28/2014	1/28/2015
24		Y	Y	Y	4/28/2008	10/23/2009	3/10/2010		1/29/2011	1/28/2014	1/28/2015
22		Y	Y	Y	4/22/2008	11/15/2009	3/30/2010		2/2/2011	2/1/2014	2/1/2015
3		Y	Y	Y	5/1/2008	11/16/2009	3/31/2010		2/3/2011	2/2/2014	2/2/2015
3		Y	Y	Y	4/8/2008	11/1/2009	3/16/2010		2/5/2011	2/4/2014	2/4/2015
3		Y	Y	Y	4/8/2008	11/1/2009	3/16/2010		2/5/2011	2/4/2014	2/4/2015
4		Y	Y	Y	6/27/2008	11/12/2009	3/27/2010		2/6/2011	2/5/2014	2/5/2015
16		Y	Y	Y	4/9/2008	11/12/2009	3/27/2010		2/7/2011	2/6/2014	2/6/2015
24		Y	Y	Y	5/2/2008	11/11/2009	3/26/2010		2/7/2011	2/6/2014	2/6/2015
14		Y	Y	Y	4/17/2008	11/11/2009	3/26/2010		2/17/2011	2/16/2014	2/16/2015
12		Y	Y	Y	6/20/2008	11/18/2009	4/2/2010		2/20/2011	2/19/2014	2/19/2015
24		Y	Y	Y	4/25/2008	11/13/2009	3/28/2010		2/20/2011	2/19/2014	2/19/2015
18		Y	Y	Y	5/6/2008	11/22/2009	4/6/2010		2/21/2011	2/20/2014	2/20/2015
19		Y	Y	Y	6/13/2008	12/11/2009	4/26/2010		2/23/2011	2/22/2014	2/22/2015
3		Y	Y	Y	5/27/2008	12/15/2009	4/30/2010		3/2/2011	3/1/2014	3/1/2015
4		Y	Y	Y	5/21/2008	11/29/2009	4/13/2010		3/2/2011	3/1/2014	3/1/2015
16		Y	Y	Y	7/28/2008	12/13/2009	4/28/2010		3/2/2011	3/1/2014	3/1/2015
16		Y	Y	Y	6/18/2008	12/16/2009	5/1/2010		3/5/2011	3/4/2014	3/4/2015
25		Y	Y	Y	5/1/2008	11/28/2009	4/12/2010		3/7/2011	3/6/2014	3/6/2015
14		Y	Y	Y	5/23/2008	12/9/2009	4/24/2010		3/9/2011	3/8/2014	3/8/2015
4		Y	Y	Y	6/12/2008	12/3/2009	4/18/2010		3/10/2011	3/9/2014	3/9/2015
4		Y	Y	Y	6/2/2008	12/23/2009	5/8/2010		3/10/2011	3/9/2014	3/9/2015
14		Y	Y	Y	5/7/2008	12/7/2009	4/22/2010		3/10/2011	3/9/2014	3/9/2015
14		Y	Y	Y	5/5/2008	12/7/2009	4/22/2010		3/11/2011	3/10/2014	3/10/2015
16		Y	Y	Y	6/18/2008	12/30/2009	5/15/2010		3/12/2011	3/11/2014	3/11/2015
25		Y	Y	Y	5/30/2008	12/25/2009	5/10/2010		3/14/2011	3/13/2014	3/13/2015
25		Y	Y	Y	5/30/2008	12/25/2009	5/10/2010		3/14/2011	3/13/2014	3/13/2015
25		Y	Y	Y	7/8/2008	12/25/2009	5/10/2010		3/14/2011	3/13/2014	3/13/2015
15		Y	Y	N	5/21/2008	12/15/2009	4/30/2010		3/15/2011	3/14/2014	3/14/2015
15		Y	Y	Y	6/16/2008	12/31/2009	5/15/2010		3/17/2011	3/16/2014	3/16/2015
16		Y	Y	Y	5/9/2008	12/8/2009	4/23/2010		3/17/2011	3/16/2014	3/16/2015
4		Y	Y	Y	5/13/2008	12/20/2009	5/5/2010		3/18/2011	3/17/2014	3/17/2015
3		Y	Y	Y	6/10/2008	12/26/2009	5/11/2010		3/21/2011	3/20/2014	3/20/2015
16		Y	Y	Y	5/20/2008	12/17/2009	5/2/2010		3/23/2011	3/22/2014	3/22/2015
23		Y	Y	Y	6/6/2008	1/5/2010	5/20/2010		3/23/2011	3/22/2014	3/22/2015
14		Y	Y	Y	6/19/2008	12/27/2009	5/12/2010		3/24/2011	3/23/2014	3/23/2015
18		Y	Y	Y	5/21/2008	12/18/2009	5/3/2010		3/27/2011	3/26/2014	3/26/2015
15		Y	Y	Y	6/17/2008	1/8/2010	5/23/2010		3/28/2011	3/27/2014	3/27/2015
3		Y	Y	Y	5/20/2008	12/26/2009	5/11/2010		3/29/2011	3/28/2014	3/28/2015
16		Y	Y	Y	8/6/2008	1/10/2010	5/25/2010		4/1/2011	3/31/2014	3/31/2015
4		Y	Y	Y	6/26/2008	12/24/2009	5/9/2010		4/2/2011	4/1/2014	4/1/2015

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	(b) (6)									
16		Y	Y	Y	Y	6/2/2008	12/26/2009	5/11/2010	4/2/2011	4/1/2014 4/1/2015
24		Y	Y	Y	Y	8/26/2008	1/11/2010	5/26/2010	4/2/2011	4/1/2014 4/1/2015
4		Y	Y	Y	Y	7/17/2008	1/4/2010	5/19/2010	4/3/2011	4/2/2014 4/2/2015
25		Y	Y	Y	Y	7/14/2008	1/19/2010	6/3/2010	4/4/2011	4/3/2014 4/3/2015
14		Y	Y	Y	Y	7/6/2008	1/8/2010	5/23/2010	4/5/2011	4/4/2014 4/4/2015
12		Y	Y	Y	Y	6/25/2008	1/15/2010	5/30/2010	4/6/2011	4/5/2014 4/5/2015
4		Y	Y	Y	Y	8/8/2008	1/14/2010	5/29/2010	4/7/2011	4/6/2014 4/6/2015
18		Y	Y	Y	Y	6/27/2008	1/1/2010	5/16/2010	4/9/2011	4/8/2014 4/8/2015
22		Y	Y	N	Y	7/23/2008	1/30/2010	6/14/2010	4/12/2011	4/11/2014 4/11/2015
25		Y	Y	N	Y	7/16/2008	1/20/2010	6/4/2010	4/12/2011	4/11/2014 4/11/2015
16		Y	Y	Y	Y	6/9/2008	1/10/2010	5/25/2010	4/16/2011	4/15/2014 4/15/2015
15		Y	Y	Y	Y	6/29/2008	1/16/2010	5/31/2010	4/17/2011	4/16/2014 4/16/2015
16		Y	Y	Y	Y	6/11/2008	1/13/2010	5/28/2010	4/18/2011	4/17/2014 4/17/2015
9		Y	Y	Y	Y	6/16/2008	1/12/2010	5/27/2010	4/19/2011	4/18/2014 4/18/2015
9		Y	Y	Y	Y	6/17/2008	1/12/2010	5/27/2010	4/19/2011	4/18/2014 4/18/2015
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16		Y	Y	Y	Y	7/15/2008	1/22/2010	6/6/2010	4/22/2011	4/21/2014 4/21/2015
25		Y	Y	Y	Y	7/10/2008	1/22/2010	6/6/2010	4/24/2011	4/23/2014 4/23/2015
25		Y	Y	Y	Y	6/27/2008	1/21/2010	6/5/2010	4/28/2011	4/27/2014 4/27/2015
16		Y	Y	Y	Y	7/18/2008	2/4/2010	6/19/2010	4/29/2011	4/28/2014 4/28/2015
16		Y	Y	Y	Y	7/9/2008	1/28/2010	6/12/2010	5/1/2011	4/30/2014 4/30/2015
25		Y	Y	Y	Y	7/7/2008	1/31/2010	6/15/2010	5/5/2011	5/4/2014 5/4/2015
3		Y	Y	Y	Y	7/11/2008	1/31/2010	6/15/2010	5/9/2011	5/8/2014 5/8/2015
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24		Y	Y	Y	Y	11/26/2008	2/8/2010	6/23/2010	5/11/2011	5/10/2014 5/10/2015
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24		Y	Y	Y	Y	9/11/2008	2/17/2010	7/2/2010	5/13/2011	5/12/2014 5/12/2015
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15		Y	Y	Y	Y	8/3/2008	2/28/2010	7/13/2010	5/20/2011	5/19/2014 5/19/2015
18		Y	Y	Y	Y	8/20/2008	2/28/2010	7/13/2010	5/24/2011	5/23/2014 5/23/2015
14		Y	Y	Y	Y	10/9/2008	3/8/2010	7/23/2010	5/26/2011	5/25/2014 5/25/2015
25		Y	Y	Y	Y	8/19/2008	2/28/2010	7/13/2010	5/26/2011	5/25/2014 5/25/2015
25		Y	Y	Y	Y	8/20/2008	2/28/2010	7/13/2010	5/26/2011	5/25/2014 5/25/2015
24		Y	Y	Y	Y	8/7/2008	2/24/2010	7/9/2010	5/27/2011	5/26/2014 5/26/2015
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19		Y	Y	Y	Y	7/29/2008	3/12/2010	7/27/2010	6/4/2011	6/3/2014 6/3/2015
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16		Y	Y	Y	Y	8/26/2008	3/5/2010	7/20/2010	6/7/2011	6/6/2014 6/6/2015
3		Y	Y	Y	Y	10/3/2008	3/20/2010	8/4/2010	6/12/2011	6/11/2014 6/11/2015
3		Y	Y	Y	Y	9/4/2008	3/20/2010	8/4/2010	6/12/2011	6/11/2014 6/11/2015
9		Y	Y	Y	Y	8/28/2008	3/21/2010	8/5/2010	6/14/2011	6/13/2014 6/13/2015
16		Y	Y	Y	Y	9/9/2008	3/18/2010	8/2/2010	6/15/2011	6/14/2014 6/14/2015
18		Y	Y	Y	Y	9/24/2008	3/24/2010	8/8/2010	6/16/2011	6/15/2014 6/15/2015
23		Y	Y		Y	9/8/2008	3/27/2010	8/11/2010	6/17/2011	6/16/2014 6/16/2015
18		Y	Y	Y	Y	9/3/2008	3/15/2010	7/30/2010	6/18/2011	6/17/2014 6/17/2015
4		Y	Y	Y	Y	10/6/2008	3/23/2010	8/7/2010	6/19/2011	6/18/2014 6/18/2015
12		Y	Y	Y	Y	10/9/2008	3/31/2010	8/15/2010	6/19/2011	6/18/2014 6/18/2015
23		Y	Y	Y	Y	9/2/2008	3/30/2010	8/14/2010	6/23/2011	6/22/2014 6/22/2015

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3	(b) (6)	Y	Y	Y	Y	9/5/2008	3/21/2010	8/5/2010	6/25/2011	6/24/2014 6/24/2015
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16		Y	Y	Y	Y	9/30/2008	4/11/2010	8/26/2010	6/28/2011	6/27/2014 6/27/2015
3		Y	Y	Y	Y	10/20/2008	4/12/2010	8/27/2010	6/29/2011	6/28/2014 6/28/2015
15		Y	Y	Y	Y	9/30/2008	4/2/2010	8/17/2010	7/3/2011	7/2/2014 7/2/2015
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26		Y	Y	Y	Y	9/2/2008	4/2/2010	8/17/2010	7/6/2011	7/5/2014 7/5/2015
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3		Y	Y	Y	Y	9/22/2008	4/19/2010	9/3/2010	7/14/2011	7/13/2014 7/13/2015
16		Y	Y	Y	Y	10/16/2008	5/1/2010	9/16/2010	7/17/2011	7/16/2014 7/16/2015
3		Y	Y	Y	Y	9/26/2008	5/2/2010	9/17/2010	7/24/2011	7/23/2014 7/23/2015
12		Y	Y	Y	Y	10/2/2008	4/22/2010	9/6/2010	7/24/2011	7/23/2014 7/23/2015
18		Y	Y	Y	Y	10/24/2008	5/7/2010	9/22/2010	7/25/2011	7/24/2014 7/24/2015
16		Y	Y	Y	Y	9/25/2008	4/26/2010	9/10/2010	7/28/2011	7/27/2014 7/27/2015
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15		Y	Y	Y	Y	1/2/2009	8/5/2010	12/20/2010	11/3/2011	11/2/2014 11/2/2015

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14		Y	Y	Y	Y	1/20/2009	8/15/2010	12/30/2010	11/6/2011	11/5/2014	11/5/2015
14		Y	Y	Y	Y	1/23/2009	8/17/2010	1/1/2011	11/14/2011	11/13/2014	11/13/2015
18		Y	Y	Y	Y	1/5/2008	8/14/2010	12/29/2010	11/18/2011	11/17/2014	11/17/2015
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16		Y	Y	Y	Y	3/20/2009	10/23/2010	3/10/2011	1/30/2012	1/29/2015	1/29/2016
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14		Y	Y	Y	Y	4/24/2009	11/19/2010	4/3/2011	2/17/2012	2/16/2015	2/16/2016
15		Y	Y	Y	Y	5/23/2009	11/29/2010	4/13/2011	2/17/2012	2/16/2015	2/16/2016
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From: Finer, Neil
To: "Wally Carlo, M.D."
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Rich, Wade
Subject: RE: SUPPORT call
Date: Monday, August 24, 2009 1:50:17 PM

Hi Wally
I will ask that we look at your groupings
Neil

Neil N. Finer, M.D.
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, August 24, 2009 10:40 AM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT call

Neil:

Sure. Yes, but we may want to look now at secondary outcomes that were pre-specifed.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, August 24, 2009 12:37 PM
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT call

Hi Wally
We only had 2 primaries – Death/BPD at 36 wks and NDI
We can certainly look at these but I doubt that we could say much in NEJM – Lets discuss this. I also want to see the interaction between Low SpO2 ands CPAP
We have a lot of work to do together!!
Be well

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Neil

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, August 24, 2009 10:29 AM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT call

Neil:

Great job to you and all.

I think a very important outcome is severity of BPD as measured by duration of ventilatory support and of O2 supplementation as well as on a vent at 36 weeks. I think these were pre-specified.

I would like to make sure we look at these.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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619 South 20th Street
525 New Hillman Building
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, August 24, 2009 11:22 AM
To: Finer, Neil; 'Cunningham, Meg'; 'alaptook@WIHRI.org'; 'Bradley Yoder'; 'Das, Abhik'; 'Gantz, Marie'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'Roger.Faix@hsc.utah.edu'; 'Wallace, Dennis'; Wally Carlo, M.D.; Rich, Wade
Cc: 'Newman, Jamie'; 'sharon.gough@hsc.utah.edu'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Martinez, Fernando; 'Huitema, Carolyn Petrie'; Marsha Sumner; 'Zaterka-Baxter, Kristin'; Starlett Williams; 'Irene, Amanda'
Subject: RE: SUPPORT call

Hello Everyone
I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik. Please find the basic demographic tables and the outcome of BPD and death etc. You will note that Death/BPD using the need for oxygen at 36 weeks as the postulated primary – because that was the data we based the study on – is significant both unadjusted and adjusted. Note that BPD is also less for the Low SpO2 group – but for that study, we need ROP which we are still waiting for.

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Congratulations on a study well done to you all and the coordinators, and RTI
Wally Wade and I will be at RTI a week today to review all the data and I have already started the first paper.
Be well
Neil

Neil N. Finer, M.D.
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Director, Division of Neonatal-Perinatal Medicine
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From: Finer, Neil
Sent: Tuesday, August 11, 2009 7:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Here are the Tables we sent to Marie

Neil N. Finer, M.D.
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Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'

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Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

Tuesday, 8/11
11:00am ET

Dial:
Within the USA
866-675-(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From:	Finer, Neil
To:	"Frantz, Ivan"; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu
Cc:	Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject:	RE: Confidential: Steering Committee Call Tuesday and Materials
Date:	Tuesday, August 25, 2009 1:29:08 PM

Hi Ivan
The protocol may say this but my understanding was always that our postulate was based on existing Network outcomes of BPD that were NOT based on the physiologic definition, and that was how we calculated the power of the study. I do not believe the Network had or used such data for the calculations for the SUPPORT trial.
In addition the physiologic requires many interpretations of infants who were or were not challenged, not all were!, requires assumptions of BPD based on nasal cannula flow or other treatments and use of these does not allow comparison of our data with any other study.
I have always assumed that we would use the conventional definition and look at the physiologic and see how clear this is. The previous assumption was that the Physiologic Definition would lower the actual BPD rate and we did not postulate that. Indeed as can be seen, the Physiologic definition resulted in very similar estimates
Our results show almost the same absolute decrease in death or BPD as the COIN trial comparing CPAP to the Controls using the same definitions – 6% for our study, 5% for COIN.
We will need further dialogue about this
Thanks
Neil

From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Tuesday, August 25, 2009 10:04 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Neil: Congratulations on pulling all this together so quickly. The data are very interesting. A comment re the abstract: The end point you report, death or BPD defined as oxygen use at 36 weeks is not the primary endpoint as written in the protocol (death or BPD by physiologic definition). The data table indicates a discrepancy between these two endpoints. We need some thought and discussion as to how to move forward with this. I look forward to hearing more this afternoon.

Ivan

From: Finer, Neil [mailto:nfiner@ucsd.edu]

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Sent: Tue 8/25/2009 11:46 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Frantz, Ivan; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

I have attached an Abstract for everyone – Very preliminary
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 25, 2009 5:33 AM
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu; Finer, Neil
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: RE: Confidential: Steering Committee Call Tuesday and Materials

Hi,
Neil will give a SUPPORT update at the beginning of the call today promptly at 3 PM!!!

Thanks
Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 25, 2009 8:26 AM
To: Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu; nfiner@ucsd.edu
Cc: Smith, Nancy M; jwaidne@emory.edu; Brenda Vecchio; gonza025@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; msumner@peds.uab.edu
Subject: Confidential: Steering Committee Call Tuesday and Materials

All – A reminder for our call today. Please see updated agenda below and attached materials.

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UPDATED: Steering Committee Conference Call Agenda 08/25/2009

1. Hydrocortisone protocol presentation (3-3:40) – Presentation and protocol attached
2. SUPPORT Update – Dr. Finer – materials attached (confidential)
3. Vitamin E Update
4. NEST Update
5. FU Bayley III motor component
6. New business

From: Cunningham, Meg
Sent: Thursday, August 20, 2009 12:43 PM
To: [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; ifrantz@tuftsmedicalcenter.org; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; 'mca113@northwestern.edu'; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; 'jon.e.tyson@uth.tmc.edu'; 'Michael Cotten'; 'rohls@salud.unm.edu'; 'Bradley.Yoder@hsc.utah.edu'; 'ambal@uab.edu'; Wallace, Dennis
Cc: Smith, Nancy M; 'jwaidne@emory.edu'; 'Brenda Vecchio'; 'gonza025@mc.duke.edu'; 'Archer, Stephanie (NIH/NICHD) [E]'; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie; Irene, Amanda; 'msumner@peds.uab.edu'
Subject: Steering Committee Call Tuesday

Dear All -

The next standing Steering Committee call is scheduled for Tuesday, August 25th at 3 PM ET.

Please Dial:
Outside the USA 1-203-310(b) (6)
or Within the USA 866-675-(b) (6)
Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 08/25/2009

7. Hydrocortisone protocol presentation (3-3:40)
8. New business

Thanks!
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org

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From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; "Cunningham, Meg"; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu
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Subject:	RE: Confidential: Steering Committee Call Tuesday and Materials
Date:	Tuesday, August 25, 2009 11:46:18 AM
Attachments:	Abstract SUPPORT Aug 25 09.doc

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Neil

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Sent: Tuesday, August 25, 2009 5:33 AM
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Michael Cotten; rohls@salud.unm.edu; Bradley.Yoder@hsc.utah.edu; ambal@uab.edu; Wallace, Dennis; srhintz@stanford.edu; Finer, Neil
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5. FU Bayley III motor component
6. New business

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Sent: Thursday, August 20, 2009 12:43 PM
To: [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; ifrantz@tuftsmedicalcenter.org; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; 'mca113@northwestern.edu'; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; 'jon.e.tyson@uth.tmc.edu'; 'Michael Cotten'; 'rohls@salud.unm.edu'; 'Bradley.Yoder@hsc.utah.edu'; 'ambal@uab.edu'; Wallace, Dennis
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Steering Committee Conference Call Agenda 08/25/2009

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8. New business

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The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Abstract

Background: The most appropriate initial and ongoing respiratory support for the extremely low birthweight infant (ELBW) has not been established by adequate prospective evidence. The current usual approaches include the early use of continuous positive airway pressure (CPAP) or the early administration of surfactant following endotracheal intubation. No study to date has compared these approaches in a large population of ELBW infants

Methods: The SUPPORT study was a randomized multicenter trial that enrolled consented preterm infants of 24 0/7ths weeks to 27 6/7ths weeks by best obstetrical within 2 prospective strata, 24 to 25 6/7ths weeks, and 26 to 27 6/7th weeks. Infants randomized to CPAP were treated with CPAP initiated in the delivery room and continued following admission to the NICU and such infants could be intubated if they met prespecified criteria including an FiO2 >.50 required to maintain an indicated SpO2 > 88% for one hour, an arterial PaCO2 > 65 torr , and/or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. Infants randomized to surfactant were intubated and received surfactant within 60 min minutes of birth. Criteria for extubation differed between the 2 groups with the CPAP infants treated using a permissive strategy allowing higher PaCO2s and extubation at higher ventilator settings. All infants were also randomized to one of 2 ranges of SpO2 while in the NICU and receiving supplemental oxygen, a low target range of 85% to 89% and a high target range of 91% to 95% using specifically altered blinded oximeters.

Results: The study enrolled 1316 infants from February 2005 to February 2009. There were 565 infants enrolled in the lower gestational age strata, and 751 in the higher strata. There were no significant differences for sex, birth weight, APGAR scores or race between the 2 groups. There were no differences between the groups in the receipt of

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any or a full course of antenatal steroids, or compressions in the DR, whereas the Surfactant group received significantly more epinephrine in the delivery room (4% vs 2%, p=0.022). In the delivery room, 66% of the CPAP infants received positive pressure ventilation compared with 93% of the surfactant infants, and surfactant was given to 14% of the CPAP versus 51% of the surfactant group, and 67% of the CPAP infants received surfactant at any time during their hospitalization, (all p<0.001). There were no differences overall for death in the delivery room or death during the hospitalization, nor any differences in length of stay, or days of oxygen for survivors, and the need for oxygen at discharge. More CPAP infants were alive and off mechanical ventilation by day 7, (p=0.015). There were no differences between the groups for airleaks including penumothoraces, and no differences for medical or surgical NEC, PDA requiring surgery, or severe IVH. All infants in the Surfactant arm were intubated, compared with only 77% of the CPAP infants required intubation during their nursery course, (p<0.001). There was a significant reduction in the use of postnatal steroids for BPD in the CPAP infants compared with the Surfactant infants , 7% vs 13%, p=0.0004). The primary outcome of death or BPD, defined as the need for supplemental oxygen at 36 weeks post conceptional age was 48% versus 54%, (p = 0.035, p= 0.042 when adjusted for gestational age, center and familial clustering). There was a significantly higher mortality (32% vs 24%, p=0.026) in the 24 to 25 weeks strata for the infants in the Surfactant arm.

Conclusions: The use of early CPAP with a permissive ventilator strategy results in a decrease in death or survival with BPD defined as the need for oxygen at 36 weeks post conceptional age compared with the use of surfactant within 1 hour of birth and a conventional mechanical ventilation approach. There were no increased adverse outcomes in the CPAP group, and the surviving infants will be followed for a complete neurodevelopmental assessment at 18 to 22 months. Early CPAP and the use of a permissive ventilator strategy is an evidence based approach for the initial respiratory support of the ELBW infant.

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From: Gail, Dorothy (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: SUPPORT call
Date: Monday, August 24, 2009 1:08:46 PM

Thank you Rose. This is great to see. Congratulations on completing the study.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, August 24, 2009 12:51 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Fw: SUPPORT call

Hi
Here is a first look at the data - please keep confidnetial!!!
Thanks for all your help!!!
Rose

Rosemary D. Higgins, MD
Program Scientist

From: Finer, Neil <nfiner@ucsd.edu>
To: Finer, Neil <nfiner@ucsd.edu>; 'Cunningham, Meg' <mcunningham@rti.org>; 'alaptook@WIHRI.org' <alaptook@WIHRI.org>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik' <adas@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; 'kurt.schibler@cchmc.org' <kurt.schibler@cchmc.org>; 'mcw3@cwru.edu' <mcw3@cwru.edu>; 'nancy newman' <nxs5@case.edu>; 'Roger.Faix@hsc.utah.edu' <Roger.Faix@hsc.utah.edu>; 'Wallace, Dennis' <dwallace@rti.org>; 'Wally Carlo, M.D.' <WCarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Cc: 'Newman, Jamie' <newman@rti.org>; 'sharon.gough@hsc.utah.edu' <sharon.gough@hsc.utah.edu>; Archer, Stephanie (NIH/NICHD) [E]; 'Brenda Vecchio' <BVecchio@WIHRI.org>; Martinez, Fernando <fmartinez@ucsd.edu>; 'Huitema, Carolyn Petrie' <petrie@rti.org>; 'msumner@peds.uab.edu' <msumner@peds.uab.edu>; 'Zaterka-Baxter, Kristin' <kzaterka@rti.org>; 'Starlett Williams' <StWilliams@peds.uab.edu>; 'Irene, Amanda' <airene@rti.org>
Sent: Mon Aug 24 12:21:49 2009
Subject: RE: SUPPORT call

Hello Everyone
I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik.
Please find the basic demographic tables and the outcome of BPD and death etc. You will note that Death/BPD using the need for oxygen at 36 weeks as the postulated primary – because that was the data we based the study on – is significant both unadjusted and adjusted. Note that BPD is also less for the Low SpO2 group – but for that study, we need ROP which we are still waiting for.
Congratulations on a study well done to you all and the coordinators, and RTI
Wally Wade and I will be at RTI a week today to review all the data and I have already started the first paper.
Be well
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine

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UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Finer, Neil
Sent: Tuesday, August 11, 2009 7:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Here are the Tables we sent to Marie

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

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Tuesday, 8/11
11:00am ET

Dial:
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866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT call
Date: Monday, August 24, 2009 12:59:35 PM

Hi Rose
Thanks for all of your support for me and this study. I would be delighted to join the call tomorrow. Can you share the email with them and I will join in whenever you want.
Let me know.
Be well
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 24, 2009 9:54 AM
To: Finer, Neil
Subject: Re: SUPPORT call

Do you want to share this with the SC tomorrow on their monthly call? The call is at 3 pm ET, or it can wait - this is your call.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Finer, Neil <nfiner@ucsd.edu>
To: Finer, Neil <nfiner@ucsd.edu>; 'Cunningham, Meg' <mcunningham@rti.org>; 'alaptook@WIHRI.org' <alaptook@WIHRI.org>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik' <adas@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; 'kurt.schibler@cchmc.org' <kurt.schibler@cchmc.org>; 'mcw3@cwru.edu' <mcw3@cwru.edu>; 'nancy newman' <nxs5@case.edu>; 'Roger.Faix@hsc.utah.edu' <Roger.Faix@hsc.utah.edu>; 'Wallace, Dennis' <dwallace@rti.org>; 'Wally Carlo, M.D.' <WCarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Cc: 'Newman, Jamie' <newman@rti.org>; 'sharon.gough@hsc.utah.edu' <sharon.gough@hsc.utah.edu>; Archer, Stephanie (NIH/NICHD) [E]; 'Brenda Vecchio' <BVecchio@WIHRI.org>; Martinez, Fernando <fmartinez@ucsd.edu>; 'Huitema, Carolyn Petrie' <petrie@rti.org>; 'msumner@peds.uab.edu' <msumner@peds.uab.edu>; 'Zaterka-Baxter, Kristin' <kzaterka@rti.org>; 'Starlett Williams' <StWilliams@peds.uab.edu>; 'Irene, Amanda' <airene@rti.org>
Sent: Mon Aug 24 12:21:49 2009
Subject: RE: SUPPORT call

Hello Everyone
I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik. Please find the basic demographic tables and the outcome of BPD and death etc. You will note that Death/BPD using the need for oxygen at 36 weeks as the postulated primary – because that was the data we based the study on – is significant both unadjusted and adjusted. Note that BPD is also less for the Low SpO2 group – but for that study, we need ROP which we are still waiting for.

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Congratulations on a study well done to you all and the coordinators, and RTI
Wally Wade and I will be at RTI a week today to review all the data and I have already started the first paper.
Be well
Neil

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San Diego, CA 92103-8774
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Facsimile: 619.543.3812

From: Finer, Neil
Sent: Tuesday, August 11, 2009 7:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
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Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'

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Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

Tuesday, 8/11
11:00am ET

Dial:
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866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
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Subject:	RE: SUPPORT call
Date:	Monday, August 24, 2009 12:21:57 PM
Attachments:	T1 Patient Description - PRELIMINARY 08-23-09.rtf T3 BPD Outcomes with adj tests - PRELIMINARY 08-21-09.rtf

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I am delighted to send you the first look at the SUPPORT Results with thanks to Marie and Abhik.
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Table 1 Patient Description for CPAP vs. Surfactant
*****PRELIMINARY DATA*****

Variable	Category	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value
GA (weeks)	24-25	43% (285/664)	43% (280/652)	0.9932
	26-27	57% (379/664)	57% (372/652)	
Male		52% (342/664)	57% (370/652)	0.0564
Race/ethnicity	Non-Hispanic Black	38% (255/664)	36% (234/652)	0.3495
	Non-Hispanic White	38% (250/664)	42% (271/652)	
	Hispanic	21% (138/664)	19% (121/652)	
	Other/unknown	3% (21/664)	4% (26/652)	
Birth weight (grams)	Mean (n=1316)	834.8 ± 188.2	825.6 ± 198.3	0.3855
Gestational age at birth (weeks)	Mean (n=1316)	26.2 ± 1.1	26.2 ± 1.1	0.6420
Apgar at 1 minute <3		23% (154/662)	26% (167/652)	0.3214
Apgar at 5 minutes <3		4% (26/664)	5% (32/652)	0.3806
PPV in the DR (per SUPP03)		66% (435/662)	93% (605/651)	<0.0001*
CPAP in the DR (per SUPP03)		81% (539/663)	22% (146/652)	<0.0001*
Surfactant in DR (per SUPP03)		14% (93/659)	51% (334/651)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		67% (443/660)	99% (645/652)	<0.0001*
Chest compressions in DR (per SUPP03)		5% (36/660)	6% (40/652)	0.5978
Epinephrine in DR (per SUPP03)		2% (13/660)	4% (27/652)	0.0222*
Antenatal steroids (any)		97% (643/664)	96% (622/651)	0.2206
Antenatal steroids (full course)		74% (486/661)	70% (452/648)	0.1300
Death in the DR (per SUPP03/SUPP04)		0% (1/663)	1% (6/652)	0.0552

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Table 1 Patient Description for CPAP vs. Surfactant
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

Characteristic	Category	CPAP (N=285)	Surfactant (N=280)	Unadjusted P-value
Male		52% (147/285)	58% (162/280)	0.1339
Race/ethnicity	Non-Hispanic Black	43% (122/285)	38% (105/280)	0.0414*
	Non-Hispanic White	32% (92/285)	43% (121/280)	
	Hispanic	22% (63/285)	16% (45/280)	
	Other/unknown	3% (8/285)	3% (9/280)	
Birth weight (grams)	Mean (n=565)	718.4 ± 124.7	698.4 ± 139.5	0.0718
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.0 ± 0.5	0.1110
Apgar at 1 minute <3		31% (88/284)	30% (84/280)	0.7993
Apgar at 5 minutes <3		7% (19/285)	7% (19/280)	0.9550
PPV in the DR (per SUPP03)		73% (206/283)	95% (267/280)	<0.0001*
CPAP in the DR (per SUPP03)		72% (205/284)	22% (62/280)	<0.0001*
Surfactant in DR (per SUPP03)		21% (59/283)	53% (149/280)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		77% (219/283)	99% (276/280)	<0.0001*
Chest compressions in DR (per SUPP03)		10% (27/284)	8% (23/280)	0.5892
Epinephrine in DR (per SUPP03)		4% (10/284)	5% (15/280)	0.2895
Antenatal steroids (any)		98% (279/285)	97% (271/279)	0.5608
Antenatal steroids (full course)		79% (224/285)	73% (202/278)	0.1009
Death in the DR (per SUPP03/SUPP04)		0% (1/284)	1% (4/280)	0.1727

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Table 1 Patient Description for CPAP vs. Surfactant
Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Characteristic	Category	CPAP (N=379)	Surfactant (N=372)	Unadjusted P-value
Male		51% (195/379)	56% (208/372)	0.2201
Race/ethnicity	Non-Hispanic Black	35% (133/379)	35% (129/372)	0.8629
	Non-Hispanic White	42% (158/379)	40% (150/372)	
	Hispanic	20% (75/379)	20% (76/372)	
	Other/unknown	3% (13/379)	5% (17/372)	
Birth weight (grams)	Mean (n=751)	922.4 ± 180.4	921.3 ± 181.5	0.9381
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.8832
Apgar at 1 minute <3		17% (66/378)	22% (83/372)	0.0959
Apgar at 5 minutes <3		2% (7/379)	3% (13/372)	0.1609
PPV in the DR (per SUPP03)		60% (229/379)	91% (338/371)	<0.0001*
CPAP in the DR (per SUPP03)		88% (334/379)	23% (84/372)	<0.0001*
Surfactant in DR (per SUPP03)		9% (34/376)	50% (185/371)	<0.0001*
Surfactant in DR or NICU (per SUPP03 & SUPP04)		59% (224/377)	99% (369/372)	<0.0001*
Chest compressions in DR (per SUPP03)		2% (9/376)	5% (17/372)	0.1042
Epinephrine in DR (per SUPP03)		1% (3/376)	3% (12/372)	0.0179*
Antenatal steroids (any)		96% (364/379)	94% (351/372)	0.2792
Antenatal steroids (full course)		70% (262/376)	68% (250/370)	0.5340
Death in the DR (per SUPP03/SUPP04)		0% (0/379)	1% (2/372)	0.1529

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Table 1. Patient Description for High vs. Low SpO2
*****PRELIMINARY DATA*****

Variable	Category	High SpO2 (N=661)	Low SpO2 (N=655)	Unadjusted p-value
GA (weeks)	24-25	43% (287/661)	42% (278/655)	0.7205
	26-27	57% (374/661)	58% (377/655)	
Male		56% (370/661)	52% (342/655)	0.1709
Race/ethnicity	Non-Hispanic Black	35% (231/661)	39% (258/655)	0.2398
	Non-Hispanic White	42% (279/661)	37% (242/655)	
	Hispanic	19% (127/661)	20% (132/655)	
	Other/unknown	4% (24/661)	4% (23/655)	
Birth weight (grams)	Mean (n=1316)	825.3 ± 193.2	835.3 ± 193.3	0.3464
Gestational age at birth (weeks)	Mean (n=1316)	26.1 ± 1.1	26.2 ± 1.1	0.4635
Apgar at 1 minute <3		26% (169/661)	23% (152/653)	0.3340
Apgar at 5 minutes <3		4% (24/661)	5% (34/655)	0.1680
PPV in the DR (per SUPP03)		81% (532/660)	78% (508/653)	0.2095
CPAP in the DR (per SUPP03)		52% (345/661)	52% (340/654)	0.9404
Surfactant in DR (per SUPP03)		34% (227/658)	31% (200/652)	0.1399
Surfactant in DR or NICU (per SUPP03 & SUPP04)		85% (557/659)	81% (531/653)	0.1229
Chest compressions in DR (per SUPP03)		6% (38/661)	6% (38/651)	0.9454
Epinephrine in DR (per SUPP03)		3% (21/661)	3% (19/651)	0.7855
Antenatal steroids (any)		96% (631/660)	97% (634/655)	0.2601
Antenatal steroids (full course)		70% (460/657)	73% (478/652)	0.1856
Death in the DR (per SUPP03/SUPP04)		1% (4/661)	0% (3/654)	0.7152

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Table 1. Patient Description for High Vs. Low SpO2
Where GA is 24-25 weeks
*****PRELIMINARY DATA*****

Characteristic	Category	High SpO2 (N=287)	Low SpO2 (N=278)	Unadjusted P-value
Male		59% (169/287)	50% (140/278)	0.0418*
Race/ethnicity	Non-Hispanic Black	37% (105/287)	44% (122/278)	0.0841
	Non-Hispanic White	41% (118/287)	34% (95/278)	
	Hispanic	18% (52/287)	20% (56/278)	
	Other/unknown	4% (12/287)	2% (5/278)	
Birth weight (grams)	Mean (n=565)	711.2 ± 134.1	705.7 ± 131.1	0.6229
Gestational age at birth (weeks)	Mean (n=565)	25.1 ± 0.5	25.1 ± 0.6	0.5523
Apgar at 1 minute <3		30% (87/287)	31% (85/277)	0.9235
Apgar at 5 minutes <3		6% (16/287)	8% (22/278)	0.2672
PPV in the DR (per SUPP03)		86% (246/286)	82% (227/277)	0.1883
CPAP in the DR (per SUPP03)		49% (140/287)	46% (127/277)	0.4857
Surfactant in DR (per SUPP03)		40% (114/286)	34% (94/277)	0.1453
Surfactant in DR or NICU (per SUPP03 & SUPP04)		91% (259/286)	85% (236/277)	0.0510
Chest compressions in DR (per SUPP03)		9% (26/287)	9% (24/277)	0.8690
Epinephrine in DR (per SUPP03)		6% (16/287)	3% (9/277)	0.1797
Antenatal steroids (any)		97% (277/286)	98% (273/278)	0.3035
Antenatal steroids (full course)		74% (211/285)	77% (215/278)	0.3612
Death in the DR (per SUPP03/SUPP04)		1% (3/287)	1% (2/277)	0.6822

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Where GA is 26-27 weeks
*****PRELIMINARY DATA*****

Characteristic	Category	High SpO2 (N=374)	Low SpO2 (N=377)	Unadjusted P-value
Male		54% (201/374)	54% (202/377)	0.9644
Race/ethnicity	Non-Hispanic Black	34% (126/374)	36% (136/377)	0.5294
	Non-Hispanic White	43% (161/374)	39% (147/377)	
	Hispanic	20% (75/374)	20% (76/377)	
	Other/unknown	3% (12/374)	5% (18/377)	
Birth weight (grams)	Mean (n=751)	912.8 ± 185.9	930.9 ± 175.4	0.1712
Gestational age at birth (weeks)	Mean (n=751)	27.0 ± 0.6	27.0 ± 0.6	0.5568
Apgar at 1 minute <3		22% (82/374)	18% (67/376)	0.1588
Apgar at 5 minutes <3		2% (8/374)	3% (12/377)	0.3743
PPV in the DR (per SUPP03)		76% (286/374)	75% (281/376)	0.5798
CPAP in the DR (per SUPP03)		55% (205/374)	56% (213/377)	0.6419
Surfactant in DR (per SUPP03)		30% (113/372)	28% (106/375)	0.5265
Surfactant in DR or NICU (per SUPP03 & SUPP04)		80% (298/373)	78% (295/376)	0.6286
Chest compressions in DR (per SUPP03)		3% (12/374)	4% (14/374)	0.6897
Epinephrine in DR (per SUPP03)		1% (5/374)	3% (10/374)	0.1922
Antenatal steroids (any)		95% (354/374)	96% (361/377)	0.4791
Antenatal steroids (full course)		67% (249/372)	70% (263/374)	0.3190
Death in the DR (per SUPP03/SUPP04)		0% (1/374)	0% (1/377)	0.9955

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Table 3. BPD outcomes for High vs. Low SpO2
*****PRELIMINARY DATA*****

Characteristic	CPAP (N=664)	Surfactant (N=652)	Unadjusted P-value	Adjusted P-value
Death by 36 weeks PMA	14% (94/664)	17% (114/652)	0.0980	0.1046
BPD (physiologic definition)	39% (225/570)	41% (220/538)	0.6302	0.8269
Death or BPD (physiologic definition) by 36 weeks	48% (319/664)	51% (334/652)	0.2480	0.2890
BPD (supplemental O2)	40% (227/570)	44% (239/538)	0.1211	0.2142
Death or BPD (supplemental oxygen) by 36 weeks	48% (321/664)	54% (353/652)	0.0354*	0.0424*

Characteristic	High SpO2 (N=661)	Low SpO2 (N=655)	Unadjusted P-value	Adjusted P-value
Death by 36 weeks PMA	14% (94/661)	17% (114/655)	0.1134	0.0821
BPD (physiologic definition)	42% (238/567)	38% (207/541)	0.2076	0.2345
Death or BPD (physiologic definition) by 36 weeks	50% (332/661)	49% (321/655)	0.6583	0.8597
BPD (supplemental O2)	46% (262/567)	38% (204/541)	0.0042*	0.0026*
Death or BPD (supplemental oxygen) by 36 weeks	54% (356/661)	49% (318/655)	0.0541	0.0830

† Adjusted p-values are adjusted for stratification by GA and center and familial clustering.

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From: Gloria Siaw
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Cotten, Mike"; "Ronald N Goldberg"; "Kimberley A Fisher"; Gantz, Marie
Subject: RE: FW: SUPPORT
Date: Saturday, August 22, 2009 1:02:41 PM

Hi Rose,

Below please find the list of the BPD queries completed. The rest should be completed in a couple of days.

Thanks.

Gloria

19 (b) (6)
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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/11/2009 01:35 PM

To "'Gloria Siaw'" <gloria.siaw@duke.edu>
cc "'Cotten, Mike'" <cotte010@mc.duke.edu>, "'Ronald N Goldberg'" <goldb008@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "Gantz, Marie" <mgantz@rti.org>
Subject RE: FW: SUPPORT

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Thanks for the update. DO you have any information regarding the BPD queries?

Regards
Rose

From: Gloria Siaw [mailto:gloria.siaw@duke.edu]
Sent: Tuesday, August 11, 2009 1:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Cotten, Mike'; 'Ronald N Goldberg'; 'Kimberley A Fisher'; Gantz, Marie
Subject: Re: FW: SUPPORT

Hi Rose,

Please see all the progress below in bold blue, we are working hard to have everything completed in a timely manner.

Thank you,

CENTER NETWORK ROP_message		
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Ophthalmologist appt. (b) (6) per subject's mother.
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Completed, have been entered into the DBMS(database)
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.Completed, have been entered into the DBMS(database)
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.Ophthalmologist appt. (b) (6) per subject's mother.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.Working on it. Two letters have been sent to subject's mother and there have been no response. Still working on it.
CENTER NETWORK FU_message		
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. NF10 and NF12 have been completed and entered into the DBMS (database)

Gloria

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/11/2009 12:01 PM

To '"Ronald N Goldberg" <goldb008@mc.duke.edu>, '"Cotten, Mike" <cotte010@mc.duke.edu>, '"gloria.siaw@duke.edu" <gloria.siaw@duke.edu>,

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"'Kimberley A Fisher'" <kimberley.fisher@duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject FW: SUPPORT

Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:53 PM
To: Ronald N Goldberg; Ricki F Goldstein; Michael Cotten; gloria.siaw@duke.edu
Cc: 'Gantz, Marie'
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

CENTER NETWORK ROP_message

19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

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19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
CENTER	NETWORK	FU_message
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

[attachment "SUPPORT BPD queries Center 19 (07-24-09).rtf" deleted by Gloria Siaw/Pediatrics/mc/Duke] [attachment "Explanation of SUPPORT BPD Queries.pdf" deleted by Gloria Siaw/Pediatrics/mc/Duke]

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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Diana Vasil; Pablo Sanchez
Cc: mcunningham@rti.org
Subject: Re: SUPPORT HEAD US"s
Date: Wednesday, August 19, 2009 3:58:48 PM

Rose,
I have complete HUS CD's for 37 study patients. The Parkland radiology department has been unable to locate 9 HUS's from 7 patients. We have written radiology reports from the missing HUS's and are attempting to locate those HUS's. We are also missing two MRI's at Children's MC which we are attempting to locate.
I will be sending the completed HUS's tonight and Meg should receive them tomorrow morning.
Thank you,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 8/14/2009 11:30 AM >>>
Hi,
We are planning the final head US central reading for SUPPORT on August 23-24. We need the following studies as soon as possible to be sent to Meg Cunningham:

Network #

Need Early

Need Late

(b) (6)

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(b) (6)

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Please let us know how you are doing - thanks for all the effort!!!

Rose
Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Support BPD queries
Date: Wednesday, August 19, 2009 12:52:10 PM

FYI

From: Gantz, Marie
Sent: Wednesday, August 19, 2009 12:36 PM
To: 'Wilson, Leslie Dawn'
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Support BPD queries

Hi Leslie,

Kris, Abhik and I had a conversation regarding the fact that Indiana uses the pregnancy wheel to calculate GA instead of using the GA at birth entered on the NG02. For purposes of SUPPORT, it is very important that we have the BPD outcome collected on all patients in a consistent manner, and since the outcome is assessed at 36 weeks PMA, we need that date to be calculated in a consistent manner (across the network) as well. So, I hate to ask you to do this, but we think it's important for the Indiana babies to have 36 weeks PMA calculated based on the NG02 GA in order to be consistent with the rest of the network, and for BPD-related data on NG07, PHY01, etc., to match that date. Please let us know if you have any questions, and also please let us know when you think you'll be able to make any necessary edits. As you know, we are working on finalizing the BPD data with the goal of having the paper submitted by the end of the year. Thanks so much for your help. We really appreciate all your hard work.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Tuesday, August 18, 2009 11:07 AM
To: Gantz, Marie
Subject: Support BPD queries

Hi Marie—The outstanding query for pt #(b) (6) has been completed. Highlighted in red –

thanks

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (pager)

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From: Das, Abhik
To: Susan Hintz
Cc: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Yao, Qing
Subject: RE: true "drop dead" date for SUPPORT MRI reading?
Date: Wednesday, August 19, 2009 12:14:33 PM

Susan:

I discussed this issue with Jenny Auman, our lead programmer. As you know, for the Hypothermia MRIs, this process took a long time. There were errors in the forms Dr. Barnes completed, and we had to make numerous changes to the forms and system to accommodate them.

Assuming this is about 500 MRIs, that you can help Dr. Barnes complete the forms as they are currently set up, and that you can look them over prior to shipping to RTI, so that errors are minimized, we think we could have the data keyed in our system, cleaned and ready for analysis, in a month. But we need to take into account that this time would be the beginning of the holiday season, so we may need to add 2 more weeks for staff out on holidays. Another 2-3 weeks would likely be needed by Qing to get some very preliminary analyses done; so we are likely talking about a lead time of around 2 months. This would of course also depend on how many forms need to be keyed for preliminary analysis -- all that you send us or only a certain number of them?

Bottom line, my thinking is that while we can shoot for a PAS late breaker, the timeline would be tight, and it is more important to have the data correct and cleaned, and the analysis done right.

Thanks

Abhik

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Tuesday, August 18, 2009 3:59 PM
To: Das, Abhik
Cc: Zaterka-Baxter, Kristin; Rosemary Higgins
Subject: true "drop dead" date for SUPPORT MRI reading?

Hi folks,

As you know, Dr. Barnes has spent and continued to spend more time than anticipated on the Hypothermia MRI project, thus making his available time for the SUPPORT MRI project extremely reduced. (He has also had a few more drains on his time that were not anticipated that are clinically and otherwise related, so it's not just the hypothermia project alone that is causing problems - don't get me wrong.) However, I am going to try to make a case to shift attention back to reading SUPPORT MRI's because I think it will be important to have at least some preliminary information to report in time for a late breakers PAS abstract. This brings me to my central question for you - if the late breakers abstract is due mid-February (submission starts 1/24 for late breakers abstracts), what would the "drop dead" date be for Dr. Barnes to finish SUPPORT MRI reading? In

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my dreams, I am thinking that if he were to start back on focused SUPPORT ASAP, read like a madman, with me cutting out as much time as possible to help him, and if I were to send in the completed forms to RTI as they are finished for data entry, it may be possible to get through SUPPORT MRI's by mid- to end or November. Would that leave enough time to look at some preliminary analyses (i.e., broad strokes about extent of white matter injury, gray matter injury, cortical and white matter maturation levels, basically stuff straight off the central reader form)?

Let me know what you think -

Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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From: Shankaran, Seetha
To: Bara, Rebecca; Higgins, Rosemary (NIH/NICHD) [E]; Sood, Beena; mgantz@rti.org
Subject: RE: FW:SUPPORT BPD queries
Date: Tuesday, August 18, 2009 4:33:01 PM

Thanks Becky
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Bara, Rebecca
Sent: Tuesday, August 18, 2009 4:31 PM
To: higginsr@mail.nih.gov; Shankaran, Seetha; Sood, Beena; mgantz@rti.org
Subject: FW: FW:SUPPORT BPD queries

Hi all,

Please see attached SUPPORT BPD query resolutions. Only NW#(b) (6) still needs medical record review to complete the updates.

Thanks,
Becky

Rebecca Bara, RN, BSN
Coordinator
NICHD Neonatal Research Network
Wayne State University
phone: 313-993-7216
pager: 313-745-(b) (6)

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From: Bara, Rebecca
Sent: Tuesday, August 11, 2009 3:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; Sood, Beena
Cc: Gantz, Marie
Subject: RE: FW:

Hi Rose,

We are almost done resolving these queries and will forward the corrections by this Thursday.

As for ROP outcomes, we have not 'Lost' these families but it has been difficult to make some contacts. For most there is no evidence of acute study outcome reached by 55 weeks PMA, so on the SUPP10 we will code that acute 55 week PMA outcome as 'Lost' because it is not known. We will continue to try making contacts and will look forward to coding the SUPP10 18 month column when we schedule/see the kids at Follow-up.

Thanks,
Becky

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 11:57 AM
To: Shankaran, Seetha; Sood, Beena; Bara, Rebecca
Cc: Gantz, Marie
Subject: FW:

Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 1:55 PM
To: 'Shankaran, Seetha'; Sood, Beena; 'Bara, Rebecca'
Cc: 'Gantz, Marie'
Subject:
Importance: High

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

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CENTER	NETWORK	ROP_message
5	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
5	(b) (6) 2	The patient is within their Fol-up window and final ROP status has not been reported.
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5	(b) (6) 1	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
CENTER	NETWORK	Other_message
5	(b) (6)	Date of death differs on NG03 and SUPP09. Please resolve inconsistency.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Bara, Rebecca
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; Sood, Beena; mgantz@rti.org
Subject: FW: FW:SUPPORT BPD queries
Date: Tuesday, August 18, 2009 4:31:03 PM
Attachments: SUPPORT BPD queries Center 5 (07-24-09) RB.rtf

Hi all,

Please see attached SUPPORT BPD query resolutions. Only NW#(b) (6) still needs medical record review to complete the updates.

Thanks,
Becky

Rebecca Bara, RN, BSN
Coordinator
NICHD Neonatal Research Network
Wayne State University
phone: 313-993-7216
pager: 313-745(b) (6)

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From: Bara, Rebecca
Sent: Tuesday, August 11, 2009 3:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; Sood, Beena
Cc: Gantz, Marie
Subject: RE: FW:

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We are almost done resolving these queries and will forward the corrections by this Thursday.

As for ROP outcomes, we have not 'Lost' these families but it has been difficult to make some contacts. For most there is no evidence of acute study outcome reached by 55 weeks PMA, so on the SUPP10 we will code that acute 55 week PMA outcome as 'Lost' because it is not known. We will continue to try making contacts and will look forward to coding the SUPP10 18 month column when we schedule/see the kids at Follow-up.

Thanks,
Becky

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 11:57 AM
To: Shankaran, Seetha; Sood, Beena; Bara, Rebecca
Cc: Gantz, Marie
Subject: FW:

Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!

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Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 1:55 PM
To: 'Shankaran, Seetha'; Sood, Beena; 'Bara, Rebecca'
Cc: 'Gantz, Marie'
Subject:
Importance: High

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose
CENTER

NETWORK

ROP_message

5

(b) (6)

The patient is within their Fol-up window and final ROP status has not been reported.

5

(b) (6)

The patient is within their Fol-up window and final ROP status has not been reported.

5

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

5

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

5

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

CENTER

NETWORK

Other_message

5

(b) (6) 2

Date of death differs on NG03 and SUPP09. Please resolve inconsistency.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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SUPPORT BPD Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	Y	.	.	O2	.	.	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			GA was 24.3 not 24.2 as 1st documented --NG02 Q,D.7 has been updated to reflect, so 36.0=05/28/07

Center ID number=5=Wayne State University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
Y	Y	N	N	. .	O2	O2	O2	None	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
Y		N	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).			NG07 updated to indicate "O2 by NC" at 36.0 weeks, FiO2 concentration has been removed.

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SUPPORT BPD Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
Y	Y	Y	Y	.	O2	O2	None	.	.	N	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
Number of days on vent/CPAP @36wks per NG07(b) (6) is greater than DOL @36wks (b) (6)	Number of days on O2 @36wks per NG07 (b) (6)) is greater than DOL @36wks (b) (6).		NG07 # of days at 36 weeks has been corrected to reflect (b) (6) days and SUPP11 days 7(b) (6) have been deleted

Center ID number=5=Wayne State University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
Y	Y	Y	Y	.	O2	O2	None	.	.	N	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 5-Wayne State University

Query 1	Query 2	Query 3	Query resolution: Center notes
Number of days on vent/CPAP @36wks per NG07 (b) (6) is greater than DOL @36wks (b) (6)	Number of days on O2 @36wks per NG07 (b)(6)) is greater than DOL @36wks (b) (6)		NG07 # of days at 36 weeks has been corrected to reflect (b)(6) days and SUPP11 days (b) (6) have been deleted. PHY01 has also been updated to reflect 36 week date as (b) (6)

Center ID number=5=Wayne State University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
N	Y	N	Y	.	RA	O2	None	.	.	N	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	On vent/CPAP @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	Infant began 36 week date in RA, went to the OR midday (intubated and O2), then returned to RA to end the day. Multiple changes have been made to the SUPP11 36 week date to reflect this.

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SUPPORT BPD Queries for Center 5-Wayne State University

Center ID number=5=Wayne State University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
Y	Y	N	N	.	O2	O2	O2	None	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
N	N	.	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).			NG07 updated to indicate on O2 by NC at 36 weeks and FiO2 concentration removed.

Center ID number=5=Wayne State University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	N	N	Y	RA	O2	N	.	N	Y

Query 1	Query 2	Query 3	Query resolution: Center notes
NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).	Any O2/RA @status is inconsistent across forms (NG07/SUPP11).	O2 by NC @status is inconsistent across forms (NG07/SUPP11).	SUPP11 status date changed to reflect "O2 by NC".

Center ID number=5=Wayne State University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

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SUPPORT BPD Queries for Center 5-Wayne State University

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	Y	.	O2	.	.	.	Y

Query 1	Query 2	Query 3	Query resolution: Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Infant was discharged on day of 36wks per NG03 but is missing 36wk snapshot on NG07.		NG07 updated to reflect data at 36 weeks. SUPP11 days 61-65 to be added when medical record available

Center ID number=5=Wayne State University Network number (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
Y	Y	N	N	.	O2	O2	O2	None	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
N	N	.	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).			NG07 updated to reflect "O2 by NC" at 36 weeks and FiO2 concentration removed.

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From: Gloria Siaw
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Cotten, Mike"; "Ronald N Goldberg"; "Kimberley A Fisher"; "Gantz, Marie"
Subject: Re: SUPPORT
Date: Monday, August 17, 2009 9:19:58 AM

Hi Rose,

Please see below for all follow-up visit update information highlighted in bold and in blue/red. We will keep you updated as soon as any new information becomes available. We know this is time sensitive issue and we are working hard to have all data collected before the count down.

Thanks,

Gloria

CENTER NETWORK ROP_message

19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Ophthalmologist appt. (b) (6) at 1:00pm per subject's mother.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. Trying hard to reach Mother for appt.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit. Trying hard to reach Mother for appt.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.Ophthalmologist appt. (b) (6) at 3:00pm per subject's mother.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.Working on it. Two letters have been sent to subject's mother and there have been no response. Still working on it.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye. Working on it get mother to bring patient for follow-up visit

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/14/2009 04:50 PM

To "'Ronald N Goldberg'" <goldb008@mc.duke.edu>, "'Cotten, Mike'" <cotte010@mc.duke.edu>, "'gloria.siaw@duke.edu'" <gloria.siaw@duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>

cc "'Gantz, Marie'" <mgantz@rti.org>

Subject SUPPORT

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Hi,
We are getting down to the wire for SUPPORT and are missing a few outcomes.
Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Friday, August 14, 2009 4:30:28 PM
Attachments: Infants with missing outcomes 08-14-09.xls
SUPPORT infants with missing ROP 08-14-09.rtf

Rose and Neil,

Attached is the list of infants who are missing primary outcome data this week and a summary of where we stand with the ROP outcome. For the BPD queries that Rose sent out, we have received responses from 8 centers that have completed the queries and I talked with another two centers today who are working on theirs. I have been working on some cross-form queries for other data items, such as IVH, and those will be ready to go out next week. Rose, do you want to send them or do you want RTI to send them? I hope to complete preliminary versions of the tables we discussed on the analysis call next week as well.

Have a good weekend.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
5	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		The patient is within their Fol-up window and final ROP status has not been reported.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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Reasons ROP is missing

The FREQ Procedure

Reason for no ROP classification				
noropreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1=Infant withdrawn	4	3.23	4	3.23
1=Estimated PMA <55 weeks	8	6.45	12	9.68
2=Lowest zone of any vessels is II at last exam	2	1.61	14	11.29
3=Lowest zone of any vessels is II at last exam	55	44.35	69	55.65
4=Lowest zone of any vessels is II for one exam	55	44.35	124	100.00

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=2=Lowest zone of any vessels is I at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
1	33	3	P	1	P	193	Y	N	3=Closed
2	47	1	2	1	2	239	Y	N	3=Closed

Reason for no ROP classification=3=Lowest zone of any vessels is II at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
3	38	2	2	2	2	56	Y		1=Not open yet
4	38	2	2	2	2	57			1=Not open yet
5	33	2	1	2	1	59			1=Not open yet
6	37	2	2	2	2	59			1=Not open yet
7	35	2	2	2	2	62			1=Not open yet
8	39	2	2	2	2	63			.
9	37	2	2	2	2	68	Y		1=Not open yet
10	33	2	.	2	.	69			1=Not open yet
11	39	2	2	2	2	71	Y		1=Not open yet
12	41	2	2	2	2	75	Y		1=Not open yet
13	42	3	2	2	2	76			1=Not open yet
14	33	2	2	2	2	77			1=Not open yet
15	35	2	2	2	2	79			1=Not open yet
16	39	2	2	2	2	79	Y		1=Not open yet
17	37	2	2	2	2	83			1=Not open yet
18	35	2	2	2	2	85			1=Not open yet
19	34	2	2	2	2	87			1=Not open yet
20	38	2	2	2	2	88			1=Not open yet
21	36	2	2	2	2	95			1=Not open yet
22	38	2	1	2	1	101	Y		1=Not open yet
23	49	2	3	2	3	105	Y		1=Not open yet
24	43	2	2	2	2	107			1=Not open yet
25	50	2	2	2	2	107	Y		1=Not open yet
26	44	2	2	2	2	107	Y		1=Not open yet
27	42	2	2	2	2	107		N	1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
28	33	2	2	2	2	109	Y		1=Not open yet
29	38	2	2	2	2	110	Y		1=Not open yet
30	36	2	2	2	2	111			1=Not open yet
31	41	2	2	2	2	115	Y		1=Not open yet
32	38	2	2	2	2	117			1=Not open yet
33	36	2	2	2	2	119	Y		2=Open now
34	32	2	1	2	1	121		N	2=Open now
35	38	2	2	2	2	123	Y		2=Open now
36	36	2	2	2	2	124			2=Open now
37	65	2	2	2	2	124	Y	?	2=Open now
38	41	2	2	2	2	130			2=Open now
39	77	2	2	2	2	132		N	2=Open now
40	34	2	2	2	2	134	Y	N	2=Open now
41	46	2	2	2	2	136		N	2=Open now
42	105	2	2	2	2	137		N	2=Open now
43	33	2	.	2	.	141	Y	N	3=Closed
44	44	2	2	2	2	143	Y		3=Closed
45	71	2	2	2	2	147		N	3=Closed
46	85	2	2	2	2	150	Y	N	3=Closed
47	55	9	2	9	2	153	Y	N	3=Closed
48	39	2	2	2	2	153			3=Closed
49	44	2	2	2	2	189	Y	N	3=Closed
50	43	2	2	2	2	200			3=Closed
51	37	2	2	2	2	203	Y	N	3=Closed
52	94	2	2	2	2	224	Y	N	3=Closed
53	34	2	2	2	2	225	Y	N	3=Closed
54	78	2	2	2	2	238	Y	N	3=Closed
55	35	2	2	2	2	245	Y	N	3=Closed
56	64	2	2	2	2	247	Y	N	3=Closed
57	36	2	2	2	2	247		N	3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=4=Lowest zone of any vessels is III for one exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained	Fu window
58	50	3	2	3	2	62			1=Not open yet
59	37	3	.	3	.	64			1=Not open yet
60	38	3	2	3	2	65			1=Not open yet
61	34	3	2	3	2	66	Y		1=Not open yet
62	36	3	.	3	.	67			1=Not open yet
63	38	3	2	3	2	68	Y		1=Not open yet
64	39	3	2	3	2	73	Y		1=Not open yet
65	40	3	2	3	2	76	Y		1=Not open yet
66	36	3	2	3	2	77	Y		1=Not open yet
67	37	3	2	3	2	80	Y		1=Not open yet
68	35	3	2	3	2	81			1=Not open yet
69	36	3	2	3	2	84	Y		1=Not open yet
70	41	3	2	3	2	88	Y		1=Not open yet
71	35	3	2	3	2	89	Y		1=Not open yet
72	41	3	2	3	2	92	Y		1=Not open yet
73	40	3	2	3	2	92	Y		1=Not open yet
74	37	3	2	3	2	96	Y		1=Not open yet
75	36	3	2	3	2	96	Y		1=Not open yet
76	38	3	2	3	2	98			1=Not open yet
77	39	3	2	3	2	98	Y		1=Not open yet
78	38	3	2	3	2	100			1=Not open yet
79	35	3	2	3	2	100	Y		1=Not open yet
80	39	3	2	3	2	103	Y		1=Not open yet
81	33	3	2	3	2	108			1=Not open yet
82	40	3	2	3	2	108	Y		1=Not open yet
83	34	3	2	3	2	109	Y		1=Not open yet
84	36	3	2	3	2	110			1=Not open yet
85	39	3	2	3	2	110			1=Not open yet
86	41	3	2	3	2	112	Y		1=Not open yet
87	34	3	2	3	2	113	Y	?	1=Not open yet
88	37	3	2	3	2	115	Y		1=Not open yet
89	36	3	2	3	2	124			2=Open now
90	48	3	2	3	2	125			2=Open now
91	44	3	2	3	2	134	Y		2=Open now

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
92	44	3	2	3	2	139			3=Closed
93	35	3	2	3	2	143	Y	N	3=Closed
94	37	3	2	3	2	153	Y	N	3=Closed
95	39	3	2	3	2	153			3=Closed
96	46	3	2	3	2	165	Y	N	3=Closed
97	36	3	2	4	2	166	Y		3=Closed
98	38	3	2	3	2	177	Y	N	3=Closed
99	44	3	2	3	2	220	Y		3=Closed
100	37	3	2	3	2	226	Y	N	3=Closed
101	55	3	2	3	2	227	Y		3=Closed
102	34	3	2	3	3	229		N	3=Closed
103	32	3	.	3	.	231	Y	N	3=Closed
104	33	3	P	3	P	233	Y	N	3=Closed
105	39	3	2	3	2	241	Y	N	3=Closed
106	36	3	2	3	2	242	Y	N	3=Closed
107	33	3	P	3	P	244	Y	N	3=Closed
108	34	3	2	3	2	245	Y	N	3=Closed
109	86	3	2	3	2	245	Y	N	3=Closed
110	39	3	2	3	2	247	Y	N	3=Closed
111	88	3	2	3	2	251	Y	N	3=Closed
112	37	3	2	3	2	255	Y	N	3=Closed

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From: Diana Vasil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPOR HEAD US"s
Date: Friday, August 14, 2009 12:55:39 PM

Rose,

We have requested the US's from Parkland and are awaiting them to compile them for us. Hopefully they will be ready shortly.

Thanks,
Diane

Diana M. Vasil RNC-NIC
UT-Southwestern Medical Center
Dept. Of Pediatrics
5323 Harry Hines Blvd.
Dallas, TX. 75390-9063
ph. 214-648-3789
fax 214-648-2481

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 8/14/2009 11:30 AM >>>
Hi,
We are planning the final head US central reading for SUPPORT on August 23-24. We need the following studies as soon as possible to be sent to Meg Cunningham:

Network #

Need Early

Need Late

(b) (6)

X

X

(b) (6)

X

X

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X

Please let us know how you are doing - thanks for all the effort!!!

Rose
Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, August 12, 2009 4:48:08 PM
Attachments: SUPPORT BPD queries Center 9 .rtf

Rose,
I have attached or progress so far. Hope to have rest soon.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 11:56 AM
To: Hale, Ellen; Barbara Stoll; Ellen Hale; Susie Buchter
Cc: Gantz, Marie
Subject: FW: SUPPORT

Hi,

Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:02 PM
To: 'Barbara Stoll'; ellen_hale@oz.ped.emory.edu; 'Susie Buchter'; 'Ira Adams-Chapman'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,

We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
N	Y	N	N	.	RA	O2	None	O2	.	Y	

PH01v1 Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status O2/RA by NC/vent/CPAP	NG07 @status O2/RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02/RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status O2 by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6)) per NG03 but SUPP11 forms are only entered through (b) (6)			Forms entered

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
N	?	N	N	.	RA	RA	None	RA	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02/RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
Y		.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center's notes
.	.	.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).			Data entry error. SUPP11 corrected

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01V1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
N	Y	N	N	.	RA	O2	RA(<=.5)	O2	.	Y	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
N	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution Center's notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01V1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	Y

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center's notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

SubQuery	Query 2	Query 3	Query resolution Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Number of days on O2 @36wks per NG07 (65) is greater than DOL @36wks (64).		NG07 corrected (addition error)

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	Y	.	.	O2	.	.	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6).			Form entered

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07 C Eligible for challenge	PH02/RA @SP11 for challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			SUPP11 entered. PH01 corrected

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07 C Eligible for challenge	PH02/RA @SP11 for challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through 04/03/07.			Form entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge?
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge?
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution: Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge?	NG07-C Eligible for challenge
Y	Y	Y	Y	.	O2	O2	None	.	.	N	

PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

Query 1	Query 2	Query 3	Query resolution Center notes
Number of days on vent/CPAP @36wks per NG07 (73) is greater than DOL @36wks (72).	Number of days on O2 @36wks per NG07 (73) is greater than DOL @36wks (72).		NG07 corrected

Center ID number=9=Emory University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	RH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	RH01v1 @36wks O2/RA(flow) by NC	NG07 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 Eligible for challenge	RH01/RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	RH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	RH01v1 @36wks O2/RA(flow) by NC	NG07 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 Eligible for challenge	RH01/RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

Center ID number=9=Emory University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	RH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	RH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

PH01 Eligible for challenge	NG07 c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
.		.	.	.	.	.	RA	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
N	.	N	Infant left hospital on [redacted] per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07 c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07 c Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

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SUPPORT BPD Queries for Center 9-Emory University

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
N	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Form entered

Center ID number=9=Emory University Network number (b) (6) **Date of 36 weeks PMA** (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	?	.	N	.	.	RA	.	RA	.	Y

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
Y	.	.	.	.	.	.	.	.

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SUPPORT BPD Queries for Center 9-Emory University

SP11 @status of by NC	NG07 @status of by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

Center ID number=9=Emory University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01V1 @36wks O2/RA(flow) by NC	NG07 Eligible for challenge
.	Y	.	N	.	.	O2	.	O2	.	N

NG07 Eligible for challenge	PH01V1 Passed challenge	SP11 @status Vent/CPAP	SP11 @status NC Vent/CPAP	NG07 @status NC Vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC Vent/CPAP	NG07 @status RA by NC Vent/CPAP
N	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status of by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			

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From: Zaterka-Baxter, Kristin
To: Ronald GOldberg
Cc: cotte010@mc.duke.edu; golds005@mc.duke.edu; kimberley.fisher@duke.edu; Gloria Siaw; kim.lutz@duke.edu; Charles Vajdl; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Brinkley, Margo F.; Auman, Jeanette O.; Huitema, Carolyn Petrie; Irene, Amanda
Subject: NICHD NRN Duke Site Visit
Date: Wednesday, August 12, 2009 2:46:59 PM
Attachments: Duke Site Visit Agenda.doc

Hi Dr. Goldberg,

Please find attached the agenda for the NICHD NRN Duke Site Visit scheduled for September 2nd and 3rd, 2009. Please let me know if you have any questions.

Thanks,
Kris

Kris Zaterka-Baxter
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3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
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RTI INTERNATIONAL | **Memorandum**

~~August 11,~~September 18,~~-~~2009

TO: Ron Goldberg, MD
Principal Investigator NICHD NRN
Duke University

FROM: Abhik Das, PhD
Principal Investigator, NICHD NRN Data Coordinating Center
RTI, Rockville, MD

SUBJECT: NICHD NRN Site Visit

Dear Dr. Goldberg,

At the request of the NICHD NRN Program Officer, Dr. Rosemary Higgins, we have scheduled a follow up site visit for Duke University on September ~~2nd and 3rd~~29,~~-~~2009 to review site performance and conduct chart reviews related to primary outcome data for the SUPPORT trial. Aside from Dr. Higgins, the monitoring team will consist of the following individuals from RTI: ~~Dr. Abhik Das, Ms. Margo Brinkley,~~ Jenny Auman(?), Carolyn Huitema, ~~Amanda Irene~~ and Kris Zaterka-Baxter.

We plan to arrive for the site visit at ~~8~~9:00 am on ~~Wednesday~~ September 29nd and leave by 4:00pm ~~on Thursday September 3rd~~. We would very much appreciate it if you can have some space available for the ~~full two days~~day for the team to conduct case reviews. A research team member should also be available (on call) to answer questions that may arise but will not need to be present during the case reviews.

The following is the tentative agenda for both days:

September 2

- NICU tour (please schedule this at your convenience and to help us avoid any unnecessary disruption on your unit)
- ~~8~~9:00 – 9:30 General overview of issues identified on prior site visit to include:~~NICU and Follow UP research organization at Duke University~~
- 9:30 – 11:00 Data collection and data flow issues
  - Data collection
  - NICU/FU data entry
  - QA/ edits
- 11:00 – 12:00 Overview of IRB
  (Documentation of recent IRB initial submission dates, revisions, and final approval dates for Late hypothermia, Term near term BP, ELBW BP, and aEEG for Duke and UNC site in addition to the INS-1 Duke Regulatory Binder)
- 12:00 – 1:00 Lunch

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- 1:00 – 5:30 Overview of chart organization and case review (please have the following records available):
  - Medical Record Charts (electronic or paper version)
  - Research Charts
  - Completed Case Report Forms
  - Regulatory Binder for the INS-1, Early BP, Preemie aEEG and Term Hypotension studies (if only available for review in your regulatory office, please schedule time at their convenience so we may review the documents)
  - Support Study Binder (all versions of the study protocol, manual and case report forms)

We will review individual patient records for the following patients:

CENTER	NETWORK	DOB (b) (6)
19	[redacted]	
19		
19		
19		
19		
19		
19		
19		
19		
19		
19		
19		
19		
19		
19		

September 3

- 9:00 – 12:00 Continuation of Case Review
- 12:00 –1:00 Lunch
- 1:00 – 3:00 Continuation of Case Review
- 3:00 – 4:00 Summary Discussion: Please allow approximately one hour towards the end of the day so the monitoring team can summarize the review and discuss any relevant findings. All research staff are invited to be present, including yourself.

Thank you in advance for helping us assure the quality and accuracy of NRN study sites Please feel free to contact me at (301) 770-8214; or adas@rti.org if you have any questions.

Cc: Rosemary Higgins, MD
Ricki Goldstein, MD
Gloria Siaw, BSN, BS, CRA
Michael Cotton, MD
Kimberly Fisher, PhD, FNP, IBCLC
Kim Lutz, RN

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Charles Vajdl

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From: Gloria Siaw
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Cotten, Mike"; "Ronald N Goldberg"; "Kimberley A Fisher"; Gantz, Marie
Subject: RE: FW: SUPPORT
Date: Wednesday, August 12, 2009 12:34:42 PM

We are working on them, and as soon as all queries are completed we will up date you.

Thanks,

Gloria

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/11/2009 01:35 PM

To "'Gloria Siaw'" <gloria.siaw@duke.edu>
cc "'Cotten, Mike'" <cotte010@mc.duke.edu>, "'Ronald N Goldberg'" <goldb008@mc.duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>, "Gantz, Marie" <mgantz@rti.org>
Subject RE: FW: SUPPORT

Thanks for the update. DO you have any information regarding the BPD queries?

Regards
Rose

From: Gloria Siaw [mailto:gloria.siaw@duke.edu]
Sent: Tuesday, August 11, 2009 1:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Cotten, Mike'; 'Ronald N Goldberg'; 'Kimberley A Fisher'; Gantz, Marie
Subject: Re: FW: SUPPORT

Hi Rose,

Please see all the progress below in bold blue, we are working hard to have everything completed in a timely manner.

Thank you,

CENTER NETWORK ROP_message

19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Ophthalmologist appt. (b) (6) per subject's mother.
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Completed, have been entered into the DBMS(database)
		No SUPP10 forms have been entered though 55 weeks PMA has been reached

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19	(b) (6)	and the infant did not die early.Completed, have been entered into the DBMS(database)
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.Ophthalmologist appt. (b) (6) [redacted] per subject's mother.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.Working on it. Two letters have been sent to subject's mother and there have been no response. Still working on it.
CENTER NETWORK		FU_message
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. NF10 and NF12 have been completed and entered into the DBMS (database)

Gloria

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

08/11/2009 12:01 PM

To "'Ronald N Goldberg'" <goldb008@mc.duke.edu>, "'Cotten, Mike'" <cotte010@mc.duke.edu>, "'gloria.siaw@duke.edu'" <gloria.siaw@duke.edu>, "'Kimberley A Fisher'" <kimberley.fisher@duke.edu>

cc "Gantz, Marie" <mgantz@rti.org>

Subject FW: SUPPORT

Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:53 PM
To: Ronald N Goldberg; Ricki F Goldstein; Michael Cotten; gloria.siaw@duke.edu
Cc: 'Gantz, Marie'
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

CENTER NETWORK ROP_message		
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
CENTER NETWORK FU_message		
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov
[attachment "SUPPORT BPD queries Center 19 (07-24-09).rtf" deleted by Gloria Siaw/Pediatrics/mc/Duke] [attachment "Explanation of SUPPORT BPD Queries.pdf" deleted by Gloria Siaw/Pediatrics/mc/Duke]

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: Duke Site Visit Agenda
Date: Tuesday, August 11, 2009 6:08:25 PM
Attachments: Final Duke Agenda.doc
Duke site visit cases for review..htm

Hi Rose,

Here is a draft of the agenda for the Duke site visit; two questions:

1. I was not sure if you wanted this agenda/memo coming from you or the DCC on your behalf so please take a look and the letter header and the text in the first paragraph
2. I was not sure if Ricki Goldstein and the new FU coordinator should be present at least for the first half of the first day and the summary at the end; if so, then I need to add them to the 'cc' line.

Additionally, attached is the email I sent Gloria earlier today so she could start to pull charts from medical records. Please note I correct the duplicate ID and notified Gloria.

Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

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RTI INTERNATIONAL | **Memorandum**

August 11, 2009

TO: Ron Goldberg, MD
Principal Investigator NICHD NRN
Duke University

FROM: Abhik Das, PhD
Principal Investigator, NICHD NRN Data Coordinating Center
RTI, Rockville, MD

SUBJECT: NICHD NRN Site Visit

Dear Dr. Goldberg,

At the request of the NICHD NRN Program Officer, Dr. Rosemary Higgins, we have scheduled a site visit for Duke University on September 2nd and 3rd 2009 to review site performance and conduct chart reviews related to primary outcome data for the SUPPORT trial. Aside from Dr. Higgins, the monitoring team will consist of the following individuals from RTI: Dr. Abhik Das, Ms. Margo Brinkley, Jenny Auman, Carolyn Huitema, Amanda Irene and Kris Zaterka-Baxter.

We plan to arrive for the site visit at 9:00 am on Wednesday September 2nd and leave by 4:00pm on Thursday September 3rd. We would very much appreciate it if you can have some space available for the full two days for the team to conduct case reviews. A research team member should also be available (on call) to answer questions that may arise but will not need to be present during the case reviews.

The following is the tentative agenda for both days:

<u>September 2</u>

- NICU tour (please schedule this at your convenience and to help us avoid any unnecessary disruption on your unit)
- 9:00 – 9:30 General overview of NICU and Follow UP research organization at Duke University
- 9:30 – 11:00 Data collection and data flow issues
  - Data collection
  - NICU/FU data entry
  - QA/ edits
- 11:00 – 11:30 Overview of IRB and medical records organization
- 11:30 – 12:30 Case review (please have the following records available):
  - Medical Record Charts (electronic or paper version)
  - Research Charts
  - Completed Case Report Forms

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- Regulatory Binder for the Early BP, Preemie aEEG and Term Hypotension studies (if only available for review in your regulatory office, please schedule time at their convenience so we may review the documents)
- Support Study Binder (all versions of the study protocol, manual and case report forms)

We will review individual patient records for the following patients:

CENTER	NETWORK	DOB
19	(b) (6)	[redacted]
19		
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19		

- 12:30 – 1:30 Lunch
- 1:30 – 5:30 Continuation of Case Review

<u>September 3</u>

- 9:00 – 12:00 Continuation of Case Review
- 12:00 –1:00 Lunch
- 1:00 – 3:00 Continuation of Case Review
- 3:00 – 4:00 Summary Discussion: Please allow approximately one hour towards the end of the day so the monitoring team can summarize the review and discuss any relevant findings. All research staff are invited to be present, including yourself.

Thank you in advance for helping us assure the quality and accuracy of NRN study sites Please feel free to contact me at (301) 770-8214; or adas@rti.org if you have any questions.

Cc: Rosemary Higgins, MD
Kimberly Fisher, PhD, FNP, IBCLC
Gloria Siaw, BSN, BS, CRA
Charles Vajdl

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From: Zaterka-Baxter, Kristin
Sent: Tuesday, August 11, 2009 2:15 PM
To: 'Gloria Siaw'
Cc: 'kimberley.fisher@duke.edu'
Subject: Duke site visit cases for review.
Hi Gloria,

These are the cases we will be reviewing. It would help tremendously if you could please flag the medical records for all data pertaining to the Support study primary outcome using posted notes in different colors for the different outcomes (i.e., red = ROP, Blue = BPD, Yellow = FU {Bayley exam}); we will be looking at data collected on the Supp05, Supp10, Supp11, NG03, NG07, PHY01, PHY02 and NF09A

CENTER	NETWORK	DOB	GEST_WKS	GEST_DYS
19	(b) (6)	[redacted]	25	1
19	(b) (6)	[redacted]	25	1
19	[redacted]	(b) (6)	27	1
19	(b) (6)	[redacted]	24	0
19	(b) (6)	[redacted]	24	6
19	(b) (6)	[redacted]	27	5
19	(b) (6)	[redacted]	27	1
19	(b) (6)	[redacted]	27	0
19	(b) (6)	[redacted]	27	5
19	(b) (6)	[redacted]	24	2
19	(b) (6)	[redacted]	24	2
19	(b) (6)	[redacted]	27	3
19	(b) (6)	[redacted]	25	3
19	(b) (6)	[redacted]	25	3
19	(b) (6)	[redacted]	25	1

In addition to the Support study chart reviews we will be reviewing the IRB documents (or where you are in the process) for:
Early BP
Preemie aEEG
Term Hypotension

The agenda will follow shortly; can you please confirm where we will be conducting the site visit (i.e., Hock Plaza?)

Thanks,
Kris

From: Gloria Siaw [mailto:gloria.siaw@duke.edu]
Sent: Tuesday, August 11, 2009 12:06 PM
To: Zaterka-Baxter, Kristin
Subject: RE: Site visit.

Hey!!.... It sounds like a plan.

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Thanks much,

Gloria

Gloria Siaw, BSN, BS, CRA
Clinical Research Coordinator
Dept of Pediatrics/Neonatology
2424 Erwin Road - Suite 504
DUMC Box 2739
Durham, NC 27705
Phone: 919 - 681- 5859
Pager: 919-970(b) (6)
Fax: 919 - 681- 4868
Email: - gloria.siaw@duke.edu

"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

08/11/2009 11:04 AM

To "Gloria Siaw" <gloria.siaw@duke.edu>
cc
Subject RE: Site visit.

Hi Gloria,

Sorry, my intent was to send them on Friday but I needed help from the statistician and programmer to make sure we are pulling the right infants; I will send them hopefully by noon today.

Sorry for the delay.
Thanks,
Kris

From: Gloria Siaw [mailto:gloria.siaw@duke.edu]
Sent: Tuesday, August 11, 2009 10:31 AM
To: Zaterka-Baxter, Kristin
Subject: Site visit.

Hey Kris,... Hope all is well. Could you please send me the list of subjects you will need to review for your visit so I can request their chart before you come. It will take me about a week or more to get all the charts from medical records. Hope to hear from you soon thanks.

Regards,

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Gloria

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Ellen Hale; Susie Buchter
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, August 11, 2009 4:35:04 PM

Rose,
I'm working on these. Give you and update tomorrow.
Ellen

Ellen Hale, RN, BS, CCRC
Neonatal Research Network
Emory University School of Medicine
Department of Pediatrics - Division of Neonatology
Office: 404-778-1679
Fax: 404-778-1467

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 11:56 AM
To: Hale, Ellen; Barbara Stoll; Ellen Hale; Susie Buchter
Cc: Gantz, Marie
Subject: FW: SUPPORT

Hi,

Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 2:02 PM
To: 'Barbara Stoll'; ellen_hale@oz.ped.emory.edu; 'Susie Buchter'; 'Ira Adams-Chapman'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,

We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Gantz, Marie
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT call
Date: Tuesday, August 11, 2009 3:54:57 PM

Thanks, Wally. I will incorporate your suggestions as I work on the tables. If anyone has any additional suggestions or comments, please let me know.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, August 11, 2009 3:42 PM
To: Finer, Neil; Gantz, Marie
Cc: higginsr@mail.nih.gov
Subject: RE: SUPPORT call

Dear Neil and Marie:

You have done a great job with the draft of the tables!

I would suggest that we start separating the tables by each treatment and control group. Thus, there would be a Table 1 for the CPAP vent study; and a Table 1 for the oxygen saturation trial. I would suggest the following:

1. Add gender and the race distribution to each of the two Tables 1.
2. Add "any surfactant" to both Tables 1.
3. Delete received PPV, surfactant DR, received chest compressions and received epinephrine from Table 1 of the oxygen saturation trial.

Table 2 for each paper should be the primary outcome as well as variations of the primary outcomes. Thus, for the ventilation study we should probably reduce the outcomes that we have on the current Table 2 to those that are the main outcomes. Alternatively, we could include primary and multiple other outcomes on the same table. It may be that we want to limit it to the primary outcomes and the pulmonary outcomes and include a Table 3 for each paper for the other outcomes such as IVH, etc.

We should list each major outcome such as NEC = 2 and IVH 3/4 by itself, as well as with the competing outcome of death.

We should also add length of stay, oxygen after discharge, and postnatal age of oxygen to the other outcomes table.

I think it is great that we are trying to finalize these tables even before we look at any results.

Best regards,
Wally

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Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 11, 2009 9:55 AM
To: 'Cunningham, Meg'; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; Marsha Sumner; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Here are the Tables we sent to Marie

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

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Tuesday, 8/11
11:00am ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6) **#**

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Lizette Torres"
Cc: "Gantz, Marie"
Subject: RE: FW: SUPPORT
Date: Tuesday, August 11, 2009 3:36:00 PM

Great

Thanks
Rose

-----Original Message-----
From: Lizette Torres [mailto:Lizette.Torres@UTSouthwestern.edu]
Sent: Tuesday, August 11, 2009 2:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: SUPPORT

Nancy from what I can see,we have no queries at this time.

Lizette Torres, RN

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 8/11/2009 10:57 AM >>>
Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 1:53 PM
To: 'Pablo.Sanchez@UTSouthwestern.edu'; 'Diana Vasil'; 'Nancy.Miller@UTSouthwestern.edu'; 'Roy Heyne'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose
CENTER

NETWORK

FU_message

4

(b) (6)

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FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, August 11, 2009 1:31:17 PM

We are waiting for a couple from Sharp. The rest were submitted today.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 11, 2009 9:02 AM
To: Finer, Neil; Rich, Wade
Cc: Gantz, Marie
Subject: FW: SUPPORT
Importance: High

Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose
FYI- we are reminding all sites we have not yet heard from

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 4:07 PM
To: 'Finer, Neil'; 'Rich, Wade'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose

CENTER	NETWORK	Other_message
22	(b) (6)	Infant is missing NG02, thus, GA at birth and date of 36 weeks PMA cannot be calculated.
22	(b) (6)	Infant died per NG03, but NG02 is incomplete (including DOB and GA) and NG07 has not been entered.
22	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Diana Vasil; Pablo Sanchez
Cc: Marie Gantz
Subject: Re: FW: SUPPORT
Date: Tuesday, August 11, 2009 1:01:10 PM

Rose,
We have ordered the charts from Medical records to answer the BPD,GDB and SUPPORT questions.
Follow-up will answer the questions about NF05 and NF09a.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206-(b)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 8/11/2009 10:57 AM >>>
Hi,
Can you let us know if you have made progress? We are anxious to have all queries resolved to move on with the analysis!!
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 24, 2009 1:53 PM
To: 'Pablo.Sanchez@UTSouthwestern.edu'; 'Diana Vasil'; 'Nancy.Miller@UTSouthwestern.edu'; 'Roy Heyne'
Cc: 'Gantz, Marie'
Subject: SUPPORT
Importance: High

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!!
Regards,
Rose
CENTER

NETWORK

FU_message

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(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT call 8/11- 11 AM ET
Date: Tuesday, August 11, 2009 11:42:38 AM

Rose,

So far we have heard back on the BPD queries from the following centers: 3 (Case), 12 (Indiana), 13 (Yale), 15 (Stanford), 16 (UAB), 21 (Rochester), 26 (UNM).

We have not heard back from: 4 (Dallas), 5 (Wayne State), 8 (Miami), 9 (Emory), 11 (Cincinnati), 14 (Brown), 18 (Houston), 19 (Duke), 22 (UCSD), 23 (Tufts), 24 (Iowa), 25 (Utah).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Gantz, Marie
Sent: Monday, August 10, 2009 12:21 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'
Cc: Cunningham, Meg; Das, Abhik
Subject: RE: SUPPORT call 8/11- 11 AM ET

Hi all,

As far as the BPD queries are concerned, we have heard back from the following centers: 3 (Case), 12 (Indiana), 13 (Yale), 15 (Stanford), 16 (UAB), 26 (UNM). For the most part it appears that the queries have been resolved at these centers, and I will be following up in the few cases where questions remain. We have yet to hear back from the other 13 centers (all centers except Wake Forest received BPD queries).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 10, 2009 10:15 AM
To: 'Finer, Neil'; Gantz, Marie
Cc: Cunningham, Meg
Subject: SUPPORT call 8/11- 11 AM ET

Neil/Marie –
Do you have items for tomorrow's call?
Thanks
Rose

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Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Finer, Neil
To: "Cunningham, Meg"; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call
Date: Tuesday, August 11, 2009 10:55:03 AM
Attachments: SUPPORT tables.doc

Here are the Tables we sent to Marie

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, August 11, 2009 6:07 AM
To: alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Martinez, Fernando; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Starlett Williams; Irene, Amanda
Subject: RE: SUPPORT call

Reminder for today's call.

From: Webb, Robin E.
Sent: Thursday, July 09, 2009 2:33 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: Newman, Jamie; '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Starlett Williams'; Irene, Amanda
Subject: SUPPORT call

The SUPPORT call to discuss data analysis and progress has been scheduled for:

Tuesday, 8/11
11:00am ET

Dial:
Within the USA
866-675-(b) (6)

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or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6) #

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Formatted: Left, Tab stops: 3.5", Centered + 4.31", Left

SUPPORT Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			
Antenatal Steroids , Any			
Antenatal Steroids, Full			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
NEC ≥ 2			
PDA requiring Surgery			
IVH Gr. III or IV or Death			
PVL			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

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Table 3. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death at 36 weeks (%) By Oxygen @ 36 wks.					
BPD or Death at 36 weeks (%) By Phys. Challenge					

Table 4. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					

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From: Finer, Neil
To: Bell, Edward; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo; Fanaroff, Avroy; Duara, Shahnaz; Navarrete, Cristina; Abhik Das
Subject: RE: Request for collaborative proposal
Date: Monday, August 10, 2009 7:07:41 PM

Perhaps we can discuss this in the call tomorrow morning since to my knowledge we do not have any data ready for analysis
Neil

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Monday, August 10, 2009 3:18 PM
To: higginsr@mail.nih.gov
Cc: Wally Carlo; Fanaroff, Avroy; Finer, Neil; Duara, Shahnaz; Navarrete, Cristina; Abhik Das
Subject: FW: Request for collaborative proposal

Rose,
OK, we need a plan to minimize exploratory analyses before the papers are published. I agree. Probably even after they are published. I'm not sure the proposal we have in mind qualifies as "exploratory". A new method for ROP screening has been proposed from Sweden (and Boston) and validated in a small Swedish population. There is a need for more validation and possibly refinement of the WINROP system.

If testing the WINROP system for ROP screening were part of the planned analysis for SUPPORT or Growth, then I understand we would have to tell Drs. Binebaum and Quinn that we cannot help them. Otherwise, why not consider the proposal for collaboration? The request we made to the Steering Committee was just for permission to share the SUPPORT and Growth protocol and data forms with our CHOP collaborators. I can help Drs. Binebaum and Quinn put together a proposal for the SUPPORT and Growth subcommittees without letting them see the protocols or forms. Is this interpretation correct? There will be no costs to the Network except RTI time and effort, so unless Abhik is concerned about the analysis effort, we don't need to submit this to the SC as a concept, right? If the subcommittees like and approve the proposal, the analyses could wait until after the planned analyses for SUPPORT and Growth are completed (unless Abhik determines it would be more efficient to do them at the same time), but waiting until after the papers are published seems unnecessary.

You probably know that there is a perception outside the Network that we are unduly protective of the data and appear self serving to some. If no one in the Network has proposed this idea until now and we tell them, "Sorry, it's a good idea, but we're not finished with our own analyses," then proceed to look at this ourselves, it will look like we stole their idea. If we tell them to wait until the SUPPORT and Growth papers are published, this may be 2 years. They'll look for other collaborators, probably Pediatrix.

The idea has considerable merit; I think the Network should be eager to collaborate with the CHOP ophthalmologists. If there is already a proposal from the SUPPORT or Growth subcommittee or Network site ophthalmologists to look at this, that's different, and I'll tell them we can't help them. If I'm out of line, please tell me. I don't know all the Network rules by chapter and verse. Can we see what the SUPPORT subcommittees think of the idea, or should we tell Binebaum and Quinn to find other collaborators and another database to use to test the WINROP system? I've attached the WINROP papers again for any who haven't seen them.
Ed

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, August 10, 2009 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu;

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aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; cotte010@mc.duke.edu; Dennis Wallace; Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Finer, Neil; Duara, Shahnaz; Navarrete, Cristina
Subject: RE: Request for collaborative proposal

We should consider putting in place mechanisms to reduce the likelihood of exploratory analyses being done before our primary and secondary papers are published.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 10, 2009 11:03 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]; 'Finer, Neil'; Duara, Shahnaz; Navarrete, Cristina
Subject: Request for collaborative proposal

Based on a recent publication Löfqvist et al from Lund (Arch Ophthalmol 2009; 127:622), Ed Bell is interested in collaborating with Drs. Binebaum and Quinn from CHOP Ophthalmology to evaluate growth rates and evolution/resolution of ROP. Please send a yes/no vote by August 17 to share the SUPPORT main trial protocol/forms as well as the growth secondary protocol/forms with the folks from CHOP.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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higginsr@mail.nih.gov

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From: Fanaroff, Avroy
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Subject: RE: Request for collaborative proposal
Date: Monday, August 10, 2009 12:38:44 PM

---

we also have superb growth data from Glutamine
Av

Avroy A. Fanaroff, M.D.
Eliza Henry Barnes Chair of Neonatology
Rainbow Babies & Children's Hospital
Professor Department of Pediatrics
Case Western Reserve University
c/o Rainbow Babies & Children's Hospital-Room 1606
11100 Euclid Avenue
Cleveland, OH 44106-6040
Phone: 216-844-3884
Fax: 216-844-1479

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 10, 2009 12:37 PM
To: 'Bell, Edward'; Fanaroff, Avroy
Subject: RE: Request for collaborative proposal

Cherrie Heller wrote a paper using the ROP data

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Monday, August 10, 2009 12:34 PM
To: Fanaroff, Avroy
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for collaborative proposal

I don't think we had good enough ROP data in Glutamine.

From: Fanaroff, Avroy [mailto:Avroy.Fanaroff@uhhospitals.org]
Sent: Monday, August 10, 2009 11:32 AM
To: Bell, Edward; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Duara, Shahnaz; Navarrete, Cristina
Subject: RE: Request for collaborative proposal

I am supportive of this effort
Could we not also go back on the Glutamine trial and examine growth or lack thereof and ROP?
Avroy

Avroy A. Fanaroff, M.D.

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Cleveland, OH 44106-6040
Phone: 216-844-3884
Fax: 216-844-1479

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Monday, August 10, 2009 12:16 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Duara, Shahnaz; Navarrete, Cristina
Subject: RE: Request for collaborative proposal

Neil et al,
Yes, the Growth secondary looks like the best database to use for this. Drs. Duara and Navarrete, would you be willing to collaborate on this project?
Ed

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, August 10, 2009 11:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]; Duara, Shahnaz; Navarrete, Cristina
Subject: RE: Request for collaborative proposal

Hi Rose
We have a growth secondary – Could the PIs from that secondary please indicate if their study was planning to look at this?
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 10, 2009 9:03 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan;

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Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]; Finer, Neil; Duara, Shahnaz; Navarrete, Cristina
Subject: Request for collaborative proposal

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Rosemary D. Higgins, MD
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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Med Watch
Date: Monday, August 10, 2009 11:53:42 AM

Sorry to get back with you so late Rose, I was(b) (6) ...They weren't study related.
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 7/30/2009 8:09 PM >>>
Were they study related?
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Nancy Miller <Nancy.Miller@UTSouthwestern.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter <kzaterka@rti.org>
Sent: Thu Jul 30 15:16:26 2009
Subject: Re: Med Watch

Rose and Kris,
I will be faxing a couple of SUPPORT Med Watches. These are infants I told you about some time ago but I just got the paperwork done. Network numbers are(b) (6) and(b) (6). Sorry these are late but they were both chronic kids and had complicated hospital courses.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "nancy newman"; mcw3@cwru.edu
Subject: RE: SUPPORT
Date: Tuesday, August 04, 2009 12:34:34 PM
Attachments: SUPPORT BPD queries Center 3 (07-24-09).doc

From: nancy newman [mailto:nxs5@case.edu]
Sent: Friday, July 31, 2009 1:32 PM
To: 'Bonnie Siner'
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 24, 2009 1:52 PM
To: mcw3@cwru.edu; nxs5@case.edu; Bonnie Siner
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!! You guys have been fantastic!!!!
Regards,
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

ENTERED.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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SUPPORT BPD Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network numbe(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge	NG07 C Eligible for challenge
N	Y	N	N	.	RA	O2	None	O2	.	Y	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution: Center notes
On/off support @36wks is inconsistent across forms (NG07/SUPP11).	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).	Baby on O_2 per nasal cannula for feeds only.Therefore, O_2 not counted on SUPP11, but for year 2005, it *was* counted on NG07.

Center ID number=3=Case Western University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge	NG07 C Eligible for challenge
.	.	.	.	.	.	.	.	.	.	.	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	N	Y	Y	RA	O2	Y	.	N	Y

Query 1	Query 2	Query 3	Query resolution: Center notes
Any O2/RA @status is inconsistent across forms (NG07/SUPP11).	RA by NC/vent/CPAP @status is inconsistent across forms (NG07/SUPP11).	O2 by NC @status is inconsistent across forms (NG07/SUPP11).	Baby on O_2 per nasal cannula for feeds only.Therefore, O_2 not counted on SUPP11, but for year 2005, it *was* counted on NG07.

Center ID number=3=Case Western University Network numbe(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA (flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA (flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

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SUPPORT BPD Queries for Center 3-Case Western University

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)			Data entry omission; data has now been entered.

Center ID number=3=Case Western University Network number (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
Y	Y	Y	Y	.	O2	O2	None	.	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
N		.	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	.	Number of days on vent/CPAP @36wks per NG07 (b) greater than DOL @36wks (b).			Error in counting. NG07 has been corrected.

Center ID number=3=Case Western University Network number (b) (6) Date of 36 weeks PMA (b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6)) per NG03 but SUPP11 forms are only entered through (b) (6)			Data entry omission; data has now been entered.

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SUPPORT BPD Queries for Center 3-Case Western University

Center ID number=3=Case Western University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01V1 @36wks O2/RA(flow) by NC	[illegible]
.	N	.	N	.	.	RA	.	None	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through 07/30/07.			Data entry omission; data has now been entered.

Center ID number=3=Case Western University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01V1 @36wks O2/RA(flow) by NC
Y	Y	N	N	.	O2	O2	O2	O2	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
N		.	.	.	.	.	.	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	.	Number of days on vent/CPAP @36wks per NG07 (b)) is greater than DOL @36wks ( ).			Error in counting. NG07 has been corrected.

Center ID number=3=Case Western University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01V1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC
Y	Y	Y	Y	.	RA	O2	None	.

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SUPPORT BPD Queries for Center 3-Case Western University

PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11@status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA
.	N		.	.	.	.	.	.

SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
.	.	.	.	Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).			On date of 36 weeks, baby on O_2 only until 0200. This is reflected on NG07. Since 1st data point on SUPP11 is at 0600, O_2 does not appear.

Center ID number=3=Case Western University Network number=(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC
.	.	.	.	.	.	.	.	.	.

PH01 Eligible for challenge	NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11@status NC/vent/CPAP	NG07@status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP
N		.	.	.	.	.	RA	.

NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution Center notes
N	.	N	Infant left hospital on (b) (6) NG03 but SUPP11 forms are entered through (b) (6)			Data entry error. SUPP11 has been corrected.

Center ID number=3=Case Western University Network number=74671 Date of 36 weeks PMA=09/15/08

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
.	Y	.	Y	.	.	O2	.	.	.	.	

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11@status NC/vent/CPAP	NG07@status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution Center notes
Infant was hospitalized @36wks (b) (6) per NG03 but SUPP11 forms are only entered through (b) (6)	Number of days on vent/CPAP @36wks per NG07 (b) is greater than DOL @36wks (b).		**Query 1-** Data entry omission. SUPP11 has been corrected. **Query 2-** Error in counting. NG07 has been corrected

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Center ID number=3=Case Western University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
Y	Y	N	N	.	RA	O2	RA(>.5)	O2	.	Y	Y

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

Query 1	Query 2	Query 3	Query resolution/center notes
Any O2/RA @36wks is inconsistent across forms (NG07/SUPP11).	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).		Challenge planned for 1 day after date of 36 weeks, but baby had weaned to room air/no support by 36 wk+1 day. Therefore no challenge necessary.

Center ID number=3=Case Western University Network number(b) (6) Date of 36 weeks PMA=(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge
.	Y	.	Y	.	.	RA	.	.	.	.

NG07-C Eligible for challenge	PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP
	.	.	.	.	.	.	.	.

SP11 @status O2 by NC	NG07 @status O2 by NC	Query 1	Query 2	Query 3	Query resolution/center notes
.	.	Infant was hospitalized @36wks(b) (6) per NG03 but SUPP11 forms are only entered through(b) (6)			Data entry error for GA on NG02 has been corrected. Therefore, 36 week date is (b) (6)

Center ID number=3=Case Western University Network number(b) (6) Date of 36 weeks PMA(b) (6)

SP11 @36wks On support	NG07 @36wks On support	SP11 @36wks Vent/CPAP	NG07 @36wks Vent/CPAP	PH01v1 @36wks Vent/CPAP	SP11 @36wks Any O2/RA	NG07 @36wks Any O2/RA	SP11 @36wks O2/RA(flow) by NC	NG07 @36wks O2/RA by NC	PH01v1 @36wks O2/RA(flow) by NC	PH01 Eligible for challenge	NG07-C Eligible for challenge
Y&N	Y	N	N	.	O2&RA	O2	None	O2	.	.	Y

PH02RA Passed challenge	SP11 @status vent/CPAP	SP11 @status NC/vent/CPAP	NG07 @status NC/vent/CPAP	SP11 @status Any O2/RA	NG07 @status Any O2/RA	SP11 @status RA by NC/vent/CPAP	NG07 @status RA by NC/vent/CPAP	SP11 @status O2 by NC	NG07 @status O2 by NC
.	.	.	.	.	.	.	.	.	.

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Query 1	Query 2	Query 3	Query Completion Comments
NG07-C is filled out but PHY01 is also expected for SUPPORT infants.	O2/RA by NC @36wks is inconsistent across forms (NG07/SUPP11/PHY01v1).		**Query 1**- PHY01 completed. **Query 2**-Data error; NG07 corrected.

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; nxs5@case.edu
Cc: "Gantz, Marie"
Subject: RE: SUPPORT
Date: Friday, July 24, 2009 1:56:07 PM

The baby below is the one seen on Wednesday and has been entered!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 24, 2009 1:52 PM
To: mcw3@cwru.edu; nxs5@case.edu; Bonnie Siner
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are getting close to having final outcomes for SUPPORT. Thanks for all your hard work. I have attached the BPD queries and an explanation for the queries to the email. In addition, we are missing the following primary outcomes for SUPPORT listed below.

Again, thanks so much for all the hard work and effort!! You guys have been fantastic!!!!
Regards,
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Antenatal_Consent_Paper_ NEJM2.doc
Date: Friday, July 24, 2009 11:05:58 AM
Attachments: Antenatal_Consent_Paper_NEJM2.doc

I rewrote the abstract to 250 works (Neil thought it was worth the experience to send it to NEJM). I just refer to NRN, since NICHD is in the header (Does that need to be "Eunice Kennedy Shirver NICHD"? I assume there is someplace where we will acknowledge the support of NHLBI in the submission.

Wade

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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Short title: Antenatal Consent in a Large Multicenter Trial

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Keywords: Informed Consent, Antenatal, Neonatal

The authors have no financial disclosures or conflicts of interest.

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ABSTRACT

Backrgound

The purpose of this study was to quantify the time, effort, and rate of success involved obtaining antenatal consent to enroll infants into the Neonatal Research Network SUPPORT trial, and to determine if these infants were representative of the eligible population.

Methods

Eligible subjects were those likely to deliver in the SUPPORT gestational age window (24-27 6/7 wks). Data included who approached them for consent, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled in the trial. Eligible, non-enrolled infants entered into the NRN Generic database were identified to allow comparison of enrolled and non-enrolled infants.

Results

2828 women were identified at 18 sites between October 2005 and February 2009. 2228 were approached for consent and 1217 (54.6%) agreed. For 77% of those approached, < 3 visits were required to complete the consent process. (mean 2.0 +/- 1.2). Of the 655 infants delivered within the study window, 610 of were enrolled. Mothers who received a neonatal consult were more likely to give consent ($p<.001$). The percentage of mothers not treated with steroids was significantly greater in the non-approached vs. the approached group (20.3%, 3.4% $p<.001$).

Conclusions:

In a trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the GA window for each one who delivered an enrolled infant. The differences between enrolled and non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

Informed consent ensures that subjects enrolled in research trials are appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represent an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery.

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled plus some time allotted for screening. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent numbers. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network. The second objective of the study was to determine whether the subjects enrolled in the trial were representative of the overall eligible population.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National

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Institute of Child Health and Human Development (NICHD). Data for this study were collected during the second half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early Continuous Positive Airway Pressure (CPAP) initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was planned.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (RTI International, Research Triangle Park, NC). Research staff collected study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached were asked if they were approached for participation in any other studies for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on

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infants between 401 and 1500g inclusive birth weight that were inborn at NRN centers or admitted to the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the eligible NRN population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. Eligible but non-enrolled infants had information collected on prenatal care, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and were otherwise eligible for participation in the SUPPORT trial. Two NRN centers did not participate in the antenatal consent trial and 4 participating centers did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were told to stop collecting data. All data collected by participating centers have been included in this analysis. Analysis using only the first 50 women from the centers that

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over-enrolled were not significantly different. Screening, enrollment and consent numbers by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Mothers were considered unable to give consent when in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 (54.6%) gave consent, and 578 subsequently delivered within the SUPPORT study window. Of these, 535 delivered infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. Mothers receiving a neonatal consult were more likely to consent ($p < .0001$), but consent was obtained during the consult in only 12%. Centers that were NICHD Maternal Fetal Medicine network centers enrolled at a higher and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways (Table 2). Infants of approached mothers were significantly more likely to be non-Hispanic white ; to be older, and to have a high school education , medical insurance, and at least one PNC visit. A

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significantly higher proportion of eligible non-enrolled infants not approached had no exposure to antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance and to have received prenatal care and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%) (Table 3).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and efforts required to approach and obtain antenatal consent from parents for the enrollment of their unborn infants. Our results reveal that 5 families needed to be identified and screened for every one infant successfully enrolled. Only 47% of women consented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. Assuming that the enrollment rate of the SUPPORT trial was equivalent in the first half (the part not included in this analysis) suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the SUPPORT trial. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found

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that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which collected data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all

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antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias, not the selection bias we have seen. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [14] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. All of these reports point toward the need to find a better method of enrolling truly representative populations in multicenter trials evaluating better practices.

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Our analysis would suggest that under-privileged subjects were less likely to participate. Because this trial enrolled subjects from 18 academic centers with long-term experience in randomized trials and a broad mix of racial, ethnic, and socio-economic populations, it is not likely that the bias involved represents an intention to include or exclude any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[15], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population enrolled as a result of antenatal consent may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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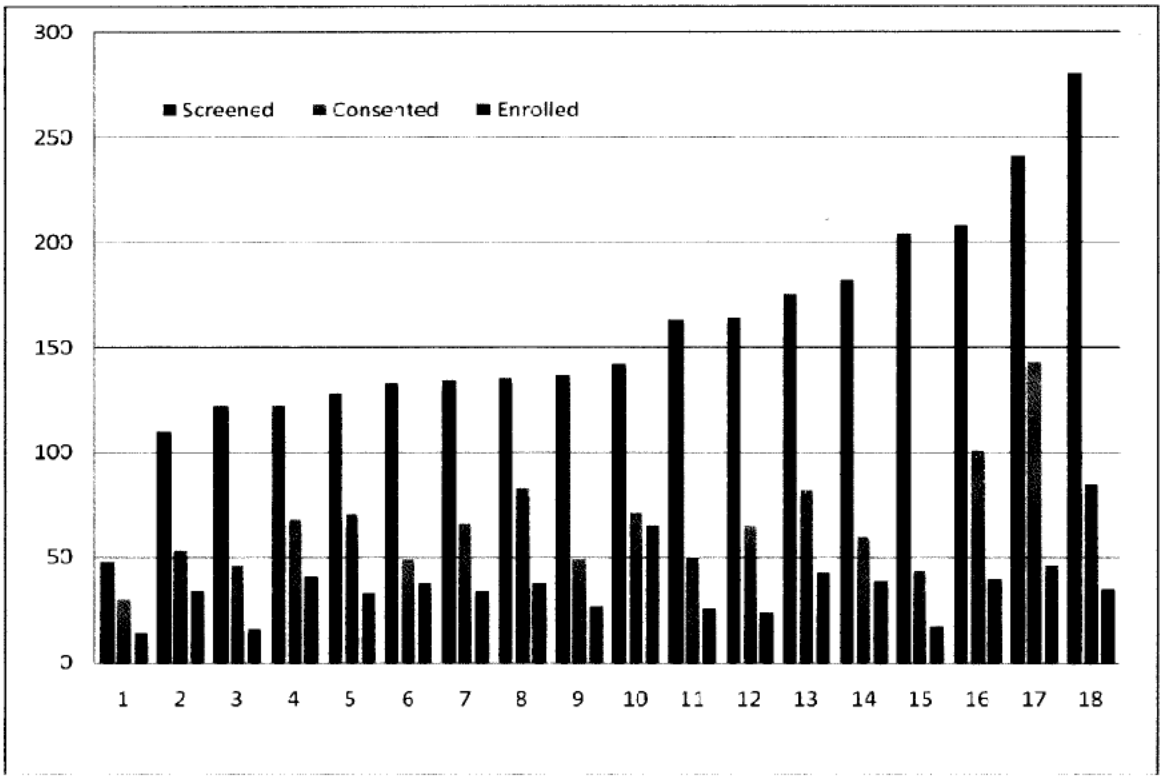

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Study staff unavailable	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 1. Reasons for not approaching mothers for consent.

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	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Enrolled Infants N=1317	Non-Enrolled Infants N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039
No Antenatal Steroids	3.8	15.7	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

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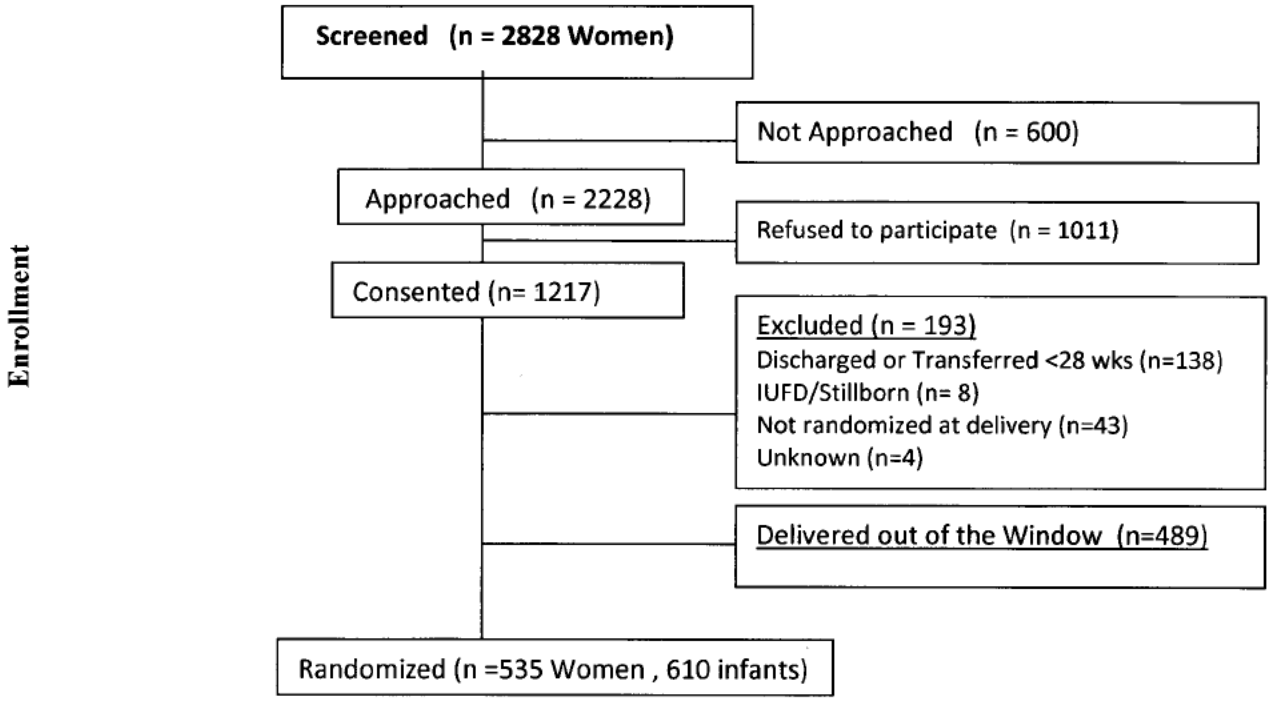

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Auman, Jeanette O.
To: Gloria Siaw
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Zaterka-Baxter, Kristin; Auman, Jeanette O.; Newman, Jamie
Subject: RE: SUPPORT infant lost to FU
Date: Thursday, July 23, 2009 4:10:00 PM

Ok, that's the problem then. Since this patient was < 1000g at birth (and their window date opened after the follow-up criteria changed), they should have had the NF forms completed. Please delete any SF forms keyed in the Support system and key them as NF forms in the 18 month Follow-up system.

This patient will also require an NF10 form keyed with the status of Lost to Follow-up. Let me know if you have any further questions!

FYI, you should not have any future Support follow-up visits that require the use of the SF forms. Only the NF forms should be used from this point onward.

Thanks,
Jenny

From: Gloria Siaw [mailto:gloria.siaw@duke.edu]
Sent: Thursday, July 23, 2009 3:31 PM
To: Auman, Jeanette O.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Gantz, Marie
Subject: RE: SUPPORT infant lost to FU

Hello Jenny,

The data entered into the system was Form SF12 V02, it was entered today. We just found out about Form NF12, NF01 we are going to enter these data into the system soon.

Thanks,

Gloria

"Auman, Jeanette O." <joa@rti.org>

07/23/2009 02:39 PM

To "Gantz, Marie" <mgantz@rti.org>, <gloria.siaw@duke.edu>
cc "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Auman, Jeanette O." <joa@rti.org>
Subject RE: SUPPORT infant lost to FU

Hi Gloria,

I don't see any Follow-up cases that could possibly be GDB ID (b) (6) in the 18 month follow-up data. Could you please take a look at the data management system and see if you can find this case? If not,

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please key the NF forms. You will enter the patient's GDB Network ID on the NF00.

Thanks,
Jenny

From: Gantz, Marie
Sent: Thursday, July 23, 2009 12:59 PM
To: gloria.siaw@duke.edu
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Auman, Jeanette O.
Subject: SUPPORT infant lost to FU

Hi Gloria,

I just spoke with Rose regarding the missing data reminders you have been receiving for SUPPORT infant (b) (6) and I think I can help clear things up. I looked up the infant's ROP data on the SUPP10 and found that the left eye was reported as mature on the (b) (6) exam. However, the right eye was reported as having the lowest zone of any vessels =2 and the highest stage in lowest zone =4 (stage 4 ROP). Because the infant had reached final status in both eyes according to the data (mature left eye, ROP in right eye), you actually did not receive a missing ROP data reminder last time (b) (6) However, if the data for the right eye are incorrect and the infant did in fact have mature vessels in the right eye as well, please edit the data accordingly.

I also tried to look at the infant's follow up data, however, I could not see that any had been entered, including the NF01, and I did not see a follow up ID for the infant. That could be because the forms have not been entered, or there could be some other issue that is preventing us to link the GDB records with the correct follow up ID. I am copying Jenny Auman, because if the latter is true she can help us figure out what the problem is.

If you have any questions, please let me know.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP f/u
Date: Thursday, July 23, 2009 3:44:34 PM

AWESOME!!!
ROSE

From: Bonnie Siner [mailto:bss5@case.edu]
Sent: Thursday, July 23, 2009 3:09 PM
To: mcw3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]; nxs5@case.edu
Cc: amt24@case.edu
Subject: SUPPORT ROP f/u

Great news!
Our last child for SUPPORT ROP outcome - Network #(b) (6) finally is COMPLETE and is being entered today!

The thanks goes to Angelia who was relentless in pursuing this mother.

Bonnie

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Wallace, Dennis
Subject: RE: SUPPORT infant lost to FU
Date: Thursday, July 23, 2009 2:00:34 PM

I have felt for a while that we should consider a full fledged site visit there.
Thanks
Abhik

Abhik Das
Senior Research Statistician
RTI International

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 23, 2009 01:39 PM Eastern Standard Time
To: Das, Abhik; Zaterka-Baxter, Kristin; Wallace, Dennis
Subject: FW: SUPPORT infant lost to FU

See the note below -

I am become concerned given the inositol urine issue and now this (which was serendipitously discovered today). I know we are really busy but perhaps we need to discuss. This was a baby before Gloria's time so may be relative to the prior coordinator.

Let me know what you think

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, July 23, 2009 1:36 PM
To: Ronald N Goldberg; Michael Cotten
Subject: FW: SUPPORT infant lost to FU

HI,

I spoke to Gloria over the phone about this SUPPORT baby. This was an infant from 2007 for whom she was trying to complete the data entry. Please see below - this child apparently had mature retina and got coded as a 4 under the ROP column (instead of the zone column) on the data entry. Thus, this infant would have been classified as severe ROP instead of resolved ROP (primary outcome of the study). Please insure that the data are being coded and keyed correctly.

Thanks for your attention to this.

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Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, July 23, 2009 12:59 PM
To: gloria.siaw@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.
Subject: SUPPORT infant lost to FU

Hi Gloria,

I just spoke with Rose regarding the missing data reminders you have been receiving for SUPPORT infant (b) (6), and I think I can help clear things up. I looked up the infant's ROP data on the SUPP10 and found that the left eye was reported as mature on the (b) (6) exam. However, the right eye was reported as having the lowest zone of any vessels =2 and the highest stage in lowest zone =4 (stage 4 ROP). Because the infant had reached final status in both eyes according to the data (mature left eye, ROP in right eye), you actually did not receive a missing ROP data reminder last time (b) (6) However, if the data for the right eye are incorrect and the infant did in fact have mature vessels in the right eye as well, please edit the data accordingly.

I also tried to look at the infant's follow up data, however, I could not see that any had been entered, including the NF01, and I did not see a follow up ID for the infant. That could be because the forms have not been entered, or there could be some other issue that is preventing us to link the GDB records with the correct follow up ID. I am copying Jenny Auman, because if the latter is true she can help us figure out what the problem is.

If you have any questions, please let me know.

Thanks,

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

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mgantz@rti.org

828-254-6255

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From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg
Subject: Re: FW: SUPPORT infant lost to FU
Date: Thursday, July 23, 2009 1:55:06 PM

---

thanks Rose....we'll check.

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

07/23/2009 01:36 PM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>

cc

Subject FW: SUPPORT infant lost to FU

HI,
I spoke to Gloria over the phone about this SUPPORT baby. This was an infant from 2007 for whom she was trying to complete the data entry. Please see below – this child apparently had mature retina and got coded as a 4 under the ROP column (instead of the zone column) on the data entry. Thus, this infant would have been classified as severe ROP instead of resolved ROP (primary outcome of the study). Please insure that the data are being coded and keyed correctly.
Thanks for your attention to this.

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, July 23, 2009 12:59 PM
To: gloria.siaw@duke.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.
Subject: SUPPORT infant lost to FU

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Hi Gloria,

I just spoke with Rose regarding the missing data reminders you have been receiving for SUPPORT infant(b) (6), and I think I can help clear things up. I looked up the infant's ROP data on the SUPP10 and found that the left eye was reported as mature on the(b) (6) exam. However, the right eye was reported as having the lowest zone of any vessels =2 and the highest stage in lowest zone =4 (stage 4 ROP). Because the infant had reached final status in both eyes according to the data (mature left eye, ROP in right eye), you actually did not receive a missing ROP data reminder last time (b) (6) However, if the data for the right eye are incorrect and the infant did in fact have mature vessels in the right eye as well, please edit the data accordingly.

I also tried to look at the infant's follow up data, however, I could not see that any had been entered, including the NF01, and I did not see a follow up ID for the infant. That could be because the forms have not been entered, or there could be some other issue that is preventing us to link the GDB records with the correct follow up ID. I am copying Jenny Auman, because if the latter is true she can help us figure out what the problem is.

If you have any questions, please let me know.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Finer, Neil
To: "Wally Carlo, M.D."; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT SUMMARY
Date: Thursday, July 16, 2009 12:27:31 PM
Attachments: 2010 ATS Noon Proposal SUPPORT Neils rev July 16.DOC

Hi Wally and Rose
I made quite extensive changes – please review
Let me know if this is appropriate
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 16, 2009 6:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: SUPPORT SUMMARY

Rose and Neil:

I have made tracked changes.

It is excellent.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 16, 2009 8:07 AM
To: nfiner@ucsd.edu; Wally Carlo, M.D.
Subject: Fw: SUPPORT SUMMARY

Please send comments
Rosemary D. Higgins, MD
Program Scientist

From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Jul 16 08:16:27 2009
Subject: RE: SUPPORT SUMMARY

Rose,

This is my draft, which I welcome you to edit. There are word limits you will notice.

Also attached is what I submitted for last year's iNO session for comparison.

I am attending a PPG review almost all day today, so after editing, I am fine for you to circulate to

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Neil and Wally (just cc me, so I know when we have the feedback and hopefully I can get this to Jim Kiley (Div Lung Diseases director) tomorrow.
The speakers (moderators) don't have to be committed yet.
If you think other literature should be here for the ATS committee to understand the field that are different than the 3 I suggested—feel free to replace.
Also, please fill in the pulse ox target ranges.

cb

Carol J. Blaisdell, M.D.
Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone
(301) 480-3451 fax
blaisdellcj@nhlbi.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 15, 2009 2:55 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: SUPPORT SUMMARY

Carol
This may e of help – the SUPPORT summary available on our website.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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This proposal has not been submitted.

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ATS 2010 * New Orleans Outside Organization Session Proposal ID:

Submitted By:	james p kiley Ph.D.	**Phone Number:**	3014350233
Institution:	Division of Lung Diseases/ National	**Fax:**	3014803547
	Heart, Lung, and Blood Institute/		
	National Institutes of Health/Dept.		
	of Health and Human Services		
E-mail Address:	kileyj@nhlbi.nih.gov		

Session Information

Title Outcomes from the NHLBI-NICHD SUPPORT Trial: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight (ELBW) Infants

Target Audience *e.g. For providers of lung health? Specific Assemblies? Serving a specific patient group or multiple groups? Will your learners have clinical, research, administrative responsibilities? Do they need to learn about areas of medicine outside of their specialty?*

pulmonologists/neonatologists/pediatricians

Should attendees have specific expertise to benefit from this session? ☒ yes (clinical) ☐ no

Session Summary Include a brief summary of the course content, from the perspective of the learner, which runs no longer than 75 words.

~~Extremely low birth weight (ELBW) premature neonates suffer from higher~~increased ~~rates of morbidity and mortality and increasing rates of pulmonary morbidity compared to term newborns.~~ Advances in therapy for the very premature ~~have~~ suggested that mode of ventilation and oxygen toxicity increase risk of bronchopulmonary dysplasia ~~(BPD)~~ and retinopathy of prematurity ~~(ROP)~~. We will present ~~Results will be presented from the~~the results of the NHLBI / NICHD SUPPORT trial ~~– a prospective, randomized, factorial 2x2 design large multi-center trial~~ that tested early CPAP and a permissive ventilation strategy versus early surfactant and a standard ~~and mechanical~~ ventilation ~~management~~ strategy and also compared a ~~with a~~ low or high pulse oximetry target on outcomes of survival without BPD, ~~and~~ ROP, and neurodevelopmental impairment.

Have you served as faculty for a similar session before? ☒ yes ☐ no

Organization Name National Heart, Lung, and Blood Institute and National Institute of Child Health, NIH

Statement of Clinical/Scientific Importance Please state in 250 words or less the educational need for this session to be presented to ATS International Conference attendees. Identify the methods you used in determining this need by checking appropriate boxes below, rather than stating them in narrative.

1 What is that difference between current and optimal practice you wish to address with education? (This is called the professional practice gap.)
2 In order to narrow or eliminate the gap will your offering increase knowledge, competence (knowing how to do something), performance in work or practice or patient health/quality of life?

1) Current practices in neonatal intensive care units for very preterm infants ~~(NICU) is variable on the~~

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include the use of early continuous positive airway pressure (CPAP) ~~as an alternative to conventional ventilation, which permits~~or the ~~-~~early use of surfactant (a known beneficial treatment to prevent respiratory distress syndrome and BPD), two approaches that have not been prospectively compared. In addition, no studies have compared the use of lower versus higher pulse oximetry targets for such infants and at present there is little high level evidence to choose between these alternatives based upon important clinical outcomes such as retinopathy of prematurity. ~~many clinicians in many~~ NICUs ~~have practices that permit oxygen saturation targets in the mid 80% range to reduce the incidence of ROP.~~

2) The SUPPORT trial was designed to ~~close the gap on knowledge of the most effective strategies for the support of breathing and oxygenation~~address these two important practices in the very preterm infant. The ~~effect~~ efficacy of the ~~alternative~~ less invasive mode of ventilation (CPAP) without early use of surfactant compared with early surfactant combined with either a low (85-89%~~—~~) ~~vs.~~or high (91-95%~~—~~) pulse oximetry ~~management~~ target has not previously been studied in ~~a~~ prospective randomized ~~fashion~~trials. Neonatal Network investigators will present the results of the SUPPORT trial which enrolled over 1300 infants and moderators will lead a discussion of the evidence, which could inform clinical practice for the ELBW infant. The ~~P~~primary outcomes ~~-~~of BPD and ROP will be presented.

Please cite 2 or 3 resources or references that could be reviewed by the Program Committee as evidence of need, if requested.

te Pas AB, Spaans VM, Rijken M, Morley CJ, Walther FJ Early nasal continuous positive airway pressure and low threshold for intubation in very preterm infants. *Acta Paediatr.* 2008 Aug;97(8):1049-54

Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH; AVIOx Study Group. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics.* 2006 Oct;118(4):1574-82

Finer N, Leone T. Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. *Pediatr Res.* 2009 Apr;65(4):375-80

What sources did you use to assess the needs of this target audience? Check all the sources that apply.

- ☐ Requests from ATS members/similar learners
- ☐ Previous course evaluation asking for suggestions
- ☐ Survey of target audience (requesting content)
- ☐ Self-assessment tests (e.g. pre-test, post test, case vignettes in surveys)
- ☐ Faculty perception
- ☐ Advice from authorities in the field
- ☐ This is a follow-up at a higher level to a previous course
- ☐ Review of literature
- ☒ New medical findings
- ☐ New guidelines
- ☐ Quality improvement data

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☐Formal needs assessment(s) by scholarly investigators

☐Other

Can these data be applied to learners at the International Conference? ☒ yes ☐ no

Objectives Please provide three learning objectives below:

Your objectives should focus on closing the gap/solving the problem you identified under the Statement of Clinical/Scientific Importance. E.g. what will the learner be able to do/do better after attending your session? You may begin some of your objectives with the following: "will be able to describe"; "will learn new findings about..."; "will appreciate the importance of...". At least one of your objectives should state how the learner will be able to apply new knowledge competence or performance/skill to his practice or work or improve quality of life or health of the patient. Eg. "will be better able to diagnose..."; "more appropriately refer..."; "refer earlier..."; "will have new strategies to manage the care of..."; "will integrate new treatment options in discussing xxx with the patient..."; "will be able to improve the quality of life/health status of his patients by xxx."

At the conclusion of this session, the learner will be able to:

1. To learn the impact of early CPAP on BPD and ROP in the SUPPORT trial
2. To learn the effect of high vs. low pulse oximetry targets on risk of BPD and ROP in the ELBW infant
3. Understand the interaction of mode of ventilation and target pulse oximetry on outcomes of BPD and ROP in ELBW infants.

Initial Disclosure of Faculty Conflicts of Interest

ATS International Conference requirements for disclosure and management of conflict of interest are based upon the ATS

Policy on Management of Conflict of Interest and **Policy on Tobacco Relationships.** Session proponents must complete the questions below as an initial disclosure. If the session is approved, session organizers, chairs and presenters will complete a detailed disclosure form and appropriate ATS oversight committees will review the disclosures as part of their oversight of sessions.

Please note:

- Many individuals have competing interests that may cause conflicts of interest. A COI depends on the situation and not on the character or actions of the individual. Examples of potential conflicts include personal financial relationships with commercial entities, or government or foundation funders, that are relevant to the session, including employment by a commercial entity; consultancy(ies); Board or Advisory Board; lecture fees; service as an expert witness; research grants; patents received or pending; royalties; and stock ownership or options (excluding mutual funds unless a sector fund concentrated in an industry[ies] relevant to the activity).
- The ATS "Policy on Tobacco Relationships" requires that individuals with a current tobacco industry relationship (or one in existence between now and the conclusion of the 2010 International Conference) not serve as a session planner (organizer), chair or presenter. (If limited to personal holdings of tobacco stocks or options, divestiture of such holdings a minimum of 30 days before the conference restores eligibility. See the policy for details.)
- Disclosure of a real or potential COI will not automatically invalidate a session proposal.

Session Proposer

1. Do you, as the proposer, have a personal financial interest(s) in a commercial entity (such as a pharmaceutical company or medical device manufacturer) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

2. Do you, as the proposer, have a personal financial interest(s) in a non-commercial entity (such as support from a government source or foundation or other non-profit source) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

3. Do you, as the proposer, have knowledge of your institution or employer having a significant financial relationship with a commercial entity that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

4. Do you, as the proposer, have a relationship with a tobacco entity at present, or may within the twelve months prior to the conference?

   ☒No ☐Yes

Proposed Faculty

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1. To your knowledge, does any other member of the proposed faculty (presenters) have a personal financial interest(s) in a commercial entity (such as a pharmaceutical company or medical device manufacturer) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

2. To your knowledge, does any other member of the proposed faculty (presenters) have a personal financial interest(s) in a non-commercial entity (such as support from a government source or foundation or other non-profit source) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

3. To your knowledge, does the institution or employer of any other member of the proposed faculty (presenters) have a significant financial relationship with a commercial entity that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

4. To your knowledge, does any other member of the proposed faculty (presenters) have a relationship with a tobacco entity at present, or may within the twelve months prior to the conference?

   ☒No ☐Yes

Topics and Faculty **Proposed Presenters and Topics**

Add Faculty (include self)

1. First Name Carol
   Middle Name J.
   Last Name Blaisdell
   Suffix
   Degrees M.D.
   Institution National Heart Lung and Blood Institute, NIH
   E-mail blaisdellcj@nhlbi.nih.gov
   ☐Chair ☒Cochair ☐ none

   ☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

2. First Name Rosemary
   Middle Name
   Last Name Higgins
   Suffix
   Degrees M.D.
   Institution National Institute of Child Health, NIH
   E-mail higginsr@mail.nih.gov
   ☐Chair ☒Cochair ☐ none

   ☒ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

3. First Name Neil
   Middle Name N.
   Last Name Finer
   Suffix
   Degrees M.D.
   Institution University of California, San Diego
   E-mail nfiner@ucsd.edu
   ☐Chair ☐Cochair ☐ none

   ☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

4. First Name Waldemar
   Middle Name A.
   Last Name Carlo
   Suffix
   Degrees M.D.
   Institution University of Alabama at Birmingham
   E-mail wcarlo@peds.uab.edu
   ☐Chair ☐Cochair ☒ none

   ☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

5. First Name Dale
   Middle Name
   Last Name Phelps
   Suffix
   Degrees
   Institution University of Rochester
   E-mail dale_phelps@urmc.rochester.edu
   ☐Chair ☐Cochair ☒ none

   ☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

6. First Name Colin
   Middle Name

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Last Name Morley
Suffix
Degrees M.D.
Institution
E-mail

☐Chair ☐Cochair ☒ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

Add Topic For each talk topic, assign a presenter listed above. You may enter up to 6 talks. Enter the length of time in minutes only

1. Presenter Rose Higgins
   Proposed Topic: Overview of SUPPORT
   Description: an overview of the NICHD network and brief introduction of the SUPPORT trial
   Length of Time (minutes) 5 minutes

2. Presenter Neil Finer
   Proposed Topic: CPAP vs. Intubation with Surfactant
   Description: Design of the study and primary outcomes related to mode of ventilator support
   Length of Time (minutes) 15 minutes

3. Presenter Waldemar Carlo
   Proposed Topic: Pulse oximetry, outcomes from high vs low targets
   Description: Design of the high vs. low pulse oximetry management strategy, and outcomes of BPD and ROP will be presented
   Length of Time (minutes) 15

4. Presenter Dale Phelps
   Proposed Topic: Moderator/Discussant
   Description Discussion of the study design and outcomes presented and facilitation of audience participation
   Length of Time (minutes) 5 minutes

5. Presenter Colin Morley
   Proposed Topic: Moderator/Discussant
   Description Discussion of the study design and outcomes presented and facilitation of audience participation
   Length of Time (minutes) 5 minutes

6. Presenter
   Proposed Topic
   Description
   Length of Time (minutes)

The ATS reserves the right to seek corporate support for all programs accepted for presentation at the International Conference.

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From: Walsh, Michele
To: Neil Finer" <; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hibbs, Anna Maria
Subject: FW: SUPPORT SDB ancillary
Date: Thursday, July 16, 2009 11:02:55 AM
Attachments: SDB ancillary study proposal revised 7.15.09.doc
Response to Critique of SDB Protocol 7.15.09.doc

HI All: Happy summer.
Attached are responses to reviewer critiques and a revised protocol
For the SUPPORT FU. I am not exactly clear on who is the
Correct person to receive the revisions. We envision this as attached
To the Breathing Outcomes followup at 6-7 yrs.

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Hibbs, Anna Maria
Sent: Wednesday, July 15, 2009 1:17 PM
To: Walsh, Michele
Subject: SUPPORT SDB ancillary

Hi Michele,

I've attached the revised protocol and my response to the protocol committee. If you could take a peak, I would really appreciate it, particularly with regards to how I have handled the "exploratory analysis" of the kids with MRI's and also the budget.

Nancy told me the standard research nurse rate was $35/hr, so I put that in my estimates, but I don't know what the standard rates are for data entry and data analysis, so I just gave time estimates.

Please let me know if there is anything I should change. Otherwise, could you send these files back to the NRN or let me know who to send them to?

THANKS! -AMH

Anna Maria Hibbs, MD, MSCE
Assistant Professor of Pediatrics
Case Western Reserve University
Rainbow Babies & Children's Hospital
(216) 844-3387

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consent of the person to whom it pertains, or as otherwise permitted by law.

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***REVISED* PROPOSAL FOR SUPPORT ANCILLARY STUDY:**

PRE-SCHOOL SLEEP-DISORDERED BREATHING

Anna Maria Hibbs, MD, MSCE

Case Western Reserve University, Rainbow Babies and Children's Hospital

RESUBMITTED July 15, 2009

Abstract/Synopsis

Premature infants are at increased risk of sleep disordered breathing (SDB) when they reach school-age (8-11 years) and young adulthood.[1, 2] SDB may adversely impact health, cognition, and behavior in children.[3-21] Furthermore, animal models and some limited human data seem to suggest that fetal and neonatal hypoxia could alter respiratory responses and lead to SDB later in life.[1, 22-35] The 5-6 year-old follow-up for the SUPPORT trial would be an ideal opportunity to (1) assess the prevalence of SDB in a large national VLBW population and (2) assess the long-term safety of lower target saturation ranges in the NICU.

Statement of Problem

SDB affects 1-2% of children.[2, 36] SDB may occur due to airway obstruction from large tonsils or abnormal airway size or tone, or it may result from altered sensing or response to hypoxia or hypercapnia. SDB has been linked to hypertension,[14] growth failure,[5] enuresis,[21, 37] and impairment of cognition, attention, and executive functions.[4, 6, 8, 11, 38-40] In fact, the association between SDB and neurocognitive abnormalities is stronger in children born preterm.[8] Identification of children at high risk for SDB and its associated morbidities is particularly important given the growing body of evidence that treatment with adenotonsillectomy may improve quality of life and neurocognitive function.[7, 15, 16, 21, 41, 42]

Children born preterm are especially vulnerable both to SDB and its sequelae. In a Finnish cohort study, very low birth weight (VLBW) infants were shown to have a two-fold risk of SDB as young adults.[1] Previously published data from the Cleveland Children's Sleep and Health Study (CCSHS) demonstrated that former preterm children have a three- to five-fold increase in the odds of SDB at 8-11 years of age compared to their term peers.[2] Furthermore, the association between sleep disordered breathing (SDB) and childhood cognitive impairment is stronger in preterm than term infants.[8] The mechanisms by which prematurity predisposes children to SDB are unknown, although there is some evidence that early exposure to hypoxia (or hyperoxia) may permanently alter respiratory responses and predispose infants to SDB later in life.[22-35]

Thus, SDB could be an important safety outcome of the target saturation arms of the SUPPORT trial. In addition, this large national cohort of preschool-aged VLBW children would be a unique opportunity to better understand the natural history of SDB in preterm infants and assess the burden of disease in this age group, as SDB has previously been documented in older children (8-11 years old) and in young adults.[1, 2]

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Hypotheses

(1) At 5-6 years of age, children born VLBW will have a higher prevalence of SDB compared to the general population.

(2) Infants randomized to the lower saturation group will have higher scores on the Sleep Related Breathing Disorder (SRDB) scale.[43, 44]

(3) *Infants randomized to CPAP will have lower scores on the SRDB scale.*

(4) Infants with more frequent desaturations *below 80%* will have higher scores on the SRDB scale.

(5) Perinatal and neonatal risk factors associated with SDB will include: black race, maternal smoking during pregnancy, *maternal hypertension* during pregnancy, and caffeine use. Gestational age, birth weight, SNAP score, days of the ventilator, and bronchopulmonary dysplasia, will not be associated with SDB.

(6) Childhood SDB will be associated with concurrent MRI abnormalities (such as hippocampal atrophy), but not with MRI abnormalities in infancy.

Specific Aims

(1) Describe the prevalence of SDB symptoms in 5-6 year old children born VLBW.

(2) Assess differences between the saturation arms of the SUPPORT study in SDB prevalence at *6-7* years of age.

(3) Determine whether infants with a higher percentage of desaturations *below 80%* are more likely to have SDB symptoms at *6-7* years of age.

(4) *Assess difference between the CPAP and intubation arms of the support study with regards to SDB prevalence at 6-7 years of age.*

(5) Determine whether previously identified risk factors for SDB in older cohorts are also risk factors for SDB in *6-7* year old VLBW children.

(6) *Explore the association between childhood SDB in VLBW infants and MRI abnormalities, at near-term and at 6-7 years of age.*

Rationale/ Background

Among infants born preterm, increased rates of SDB have been documented at school age and in young adulthood.[1, 26] In the CCSHS cohort, traditional markers of neonatal severity -- such as lower birth weight, days on the ventilator, BPD, and sepsis -- were not associated with an increased risk of SDB.[26] Black race and having a single mother were associated with increased risk of SDB, suggesting both genetic and socioeconomic factors may play a role. In race-adjusted analyses, mild maternal pre-eclampsia was significantly associated with an increased odds of SDB [OR 7.56 (1.66-34.48). A history of xanthine use was significant in unadjusted analyses [OR 2.43 (1.01-5.87)], with a

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race-adjusted odds ratio of 1.94 (0.79-4.78). An association with xanthines could potentially indicate either a medication effect or be a marker of certain patients with underlying life-long differences in respiratory drive manifesting as both SDB and apnea of prematurity. Alternatively, xanthines may be a marker of neonatal apnea and intermittent hypoxia; pre-ecclampsia itself may be a marker of *in utero* hypoxia and/or ischemia. Similarly, maternal smoking during pregnancy may cause placental insufficiency and fetal hypoxia. In the young adults born VLBW, Paavonen et al found that maternal smoking during pregnancy was associated with SDB [OR 2.64 (1.17-5.97)].[1] Although maternal smoking during pregnancy was not a statistically significant risk factor for SDB in the CCSHS cohort, the point estimate was similar [OR 2.09 (0.96-4.55)].[26] If early hypoxia does indeed put preterm infants at increased risk for SDB later in life, the SUPPORT population would be an ideal group in which to test this hypothesis, both by assessing differences in SDB between the two saturation groups, as well as by assessing whether an increased amount of time spent below the targeted saturation ranges was associated with SDB.

Intubation and degree and duration of respiratory support could be important risk factors and/or potential confounders. In the Finnish study of young adults, there was no association between SDB and a history of mechanical ventilation.[1] However, in the Cleveland Children's Sleep and Health Study (CCSHS), there was a non-significant suggestion that there may in fact be an association between degree of neonatal respiratory support and subsequent SDB; compared to infants with no respiratory support, the odds of SDB for children on oxygen or CPAP was 2.31 (0.23-23.30) and for infants with a history of intubation 3.74 (0.49-28.67).[26] It may be that in the larger SUPPORT population, such an association would be identified, and the SUPPORT trial would be an ideal population in which to address this question.

Both prematurity and SDB are associated with MRI changes.[11, 45-52] While the current literature does not support a link between neonatal ultrasound abnormalities and subsequent SDB, near-term MRI findings have not been assessed. In addition there is some evidence that SDB is associated with concurrent MRI changes, although many authors suggest that the SDB causes the neuroimaging changes. However, no one specific MRI abnormality is consistently reported. Using magnetic resonance spectroscopy (MRSI) Hallbower showed differences in hippocampal neuronal metabolism in children with SDB[11]. In addition, in adults, there is some mixed data suggesting a variety of detectable brain difference in the MRI's of patients with SDB, including lower fractional anisotrophy on diffusion tensor imaging, hippocampal atrophy, and other lesions.[48, 52] In addition, in the CCSHS, children born preterm were found to be more vulnerable to the neurocognitive effects of SDB; childhood neuroimaging was not done in this cohort.[8] It is unknown whether, in a preterm population, either near-term MRI abnormalities or concurrent MRI abnormalities in childhood are associated with SDB.

Methods: A validated 1-page questionnaire will be administered to the parent(s) at follow-up.[43, 44] Thus one-page questionnaire, the Sleep-Related Breathing Disorder (SRBD) scale of the Pediatric Sleep Questionnaire, has been shown to predict polysomnographic results with an accuracy useful for research, although it is not sufficiently accurate to substitute for polysomnography in individual patient care. The SRDB scale has three subscales, including a 4-item sleepiness scale, a 4-item snoring scale, and a 6-item inattention/hyperactivity scale. All questions responses are "yes" = 1, "no" = 0 and "don't know." An average question score $\geq$0.33 has been used to identify SDB.

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We anticipate that the questionnaire will take ≤15 minutes to complete. *We propose that the questionnaire be administered by phone 1-6 weeks before the 6-7 year exam. This phone-call can also serve as a reminder call, and its proximity will allow correlation with other variables gathered at the 6-7 year exam, such as BMI.*

Study Design/ Definition of Population: This ancillary study will add a brief questionnaire to the planned 5-6 year follow-up assessment of the children *enrolled in the Breathing Outcomes* study 6-7 yr follow-up in the SUPPORT trial.

Inclusion criteria:

- *$24^{0/7}$-$27^{6/7}$ weeks gestation at birth*
- *Enrolled in SUPPORT*
- *Enrollment in the Breathing Outcomes follow-up*

Exclusion criteria

- *Major congenital malformations*
- *Failure to consent for Breathing Outcomes follow-up at 6-7 yrs*

This study will be linked to the Breathing Outcomes Follow-Up at 6-7 years of age. An analysis of differences between infants who presented to follow-up and those who were initially enrolled in the Breathing Outcomes study but did not follow-up will be performed. Key variables to assess differences will include gestational age, birthweight, race, sex, BPD, and the interventions to which they were initially randomized.

Description of Intervention: A validated, one-page, 22-item sleep-questionnaire will be administered to the parent(s).[43, 44] We estimate that it will take 10-15 minutes to complete, as described above.

Primary and Secondary Outcomes: The primary outcome will be SDB as defined by an average score of ≥0.33 on the SRBD scale. Secondary outcomes will be the actual score on the scale, and the distribution of answers to specific questions and domains within the questionnaire.

Sample Size: The SUPPORT trial aims to enroll 1310 infants born between $24^{0/7}$ and $27^{6/7}$ weeks gestation. *The Breathing Outcomes study is expected to follow-up 750 children at age 6-7 years.*

The following calculations are based on *750* infants, with a power of 0.8, and alpha of 0.05:

Estimate of Prevalence: The width of the confidence intervals for ascertaining the prevalence of SDB in the SUPPORT population is presented. At 8-11 years of age, between 4.3% and 7.4% of preterm children have SDB.[2] Most estimates of childhood SDB prevalence in the general population are 1-2%.[2, 36] The following table shows the 95% confidence intervals for a range of possible prevalence

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rates for SDB in the SUPPORT trial. There would be sufficient power to find a significant difference between historical estimates of SDB prevalence in the general population and the SDB prevalence in the SUPPORT trial if the SUPPORT SDB prevalence is approximately 4% or higher.

Overall SDB prevalence	95% Confidence Interval
4% (n=*30*)	*2.6-5.4%*
6% (n=*45*)	*4.3-7.7%*
8% (n=*60*)	*6.1-9.9%*

Differences between groups: The detectable differences between groups are listed below, assuming a chi-squared test to detect differences in the prevalence of SDB. *For instance, if the baseline prevalence of SDB in the higher saturation arm is 6%, we would be able to detect a relative risk of 2.2 for lower saturations. Similarly, if the baseline rate of SDB in the CPAP arm is 8%, we would be able to detect a relative risk of 2.0 for randomization to intubation at delivery.*

Baseline Prevalence of SDB	Detectable Relative Risk
4%	*2.5*
6%	*2.2*
8%	*2.0*

We can also calculate the detectable difference between the groups using a t-test for difference in the mean SRDB scores in the two groups. Assuming a SRDB score standard deviation of 0.21,[44] we would be able to detect mean difference in scores of 0.04 between the two groups.

The following calculations are for an exploratory analysis of the association between MRI findings and SDB, based on an alpha of 0.05, a power of 0.8, and an N of 350, a conservative estimate of the infants enrolled in both the Breathing Outcomes and MRI follow-up studies:

The detectable relative risks are listed below, assuming a chi-squared test to detect differences in the prevalence of SDB in infants with MRI abnormalities. The range of the incidence of MRI abnormailites listed is based on recent reports of abnormalities in 75-95% of near-term MRIs.[45, 50] Moderate to severe findings have been reported in approximately 12%.[50]

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Baseline Prevalence of MRI Abnormalities	***Baseline Incidence of SDB***		
	4%	***6%***	***8%***
10%	5.0	4.2	3.7
15%	4.2	3.6	3.2
75%	4.0	3.3	2.9
85%	4.2	3.6	3.2

Tests of continuous, as opposed to binary, differences in MRI findings would be more powerful. To assess differences in hippocampal volume in infants with and without SDB, we calculated the detectable difference in volumes for a t-test assuming an alpha of 0.05 and power of 0.8. For a range in SDB frequency between 10% and 4% in the total cohort, the detectable difference in volumes ranges from 0.49 to 0.77 of a standard deviation.

Available population: The proposed questionnaire will be administered to children participating in the SUPPORT study Breathing Outcomes follow-up at preschool age. The short questionnaire will only represent a minimal additional burden on the participants.

Recruitment: No additional recruitment resources would be needed for this ancillary study. *The phone-calls prior to the scheduled follow-up visit may aide retention and follow-up of infants enrolled in the Breathing Outcomes follow-up.*

Budget and Time Estimates:

Costs include research nurse time, data entry, and data analysis. We estimate:

- Approximately 20 minutes research nurse time per survey, as multiple phone calls may be necessary to reach a family.
    - 1/3 x 750 = 250 hrs.
    - At $35/hr this would equal 250 x $35 = $8,750
- Approximately 5 minutes per survey for data entry.
    - 1/12 x 750 = 62.5 hrs
- Approximately 12 hours of analysis time required.

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SLEEP-RELATED BREATHING DISORDER SCALE

While sleeping, does your child…

	Yes	No	Not Sure
(1) Snore more than half the time?			
(2) Always snore?			
(3) Snore loudly?			
(4) Have "heavy" or "loud" breathing?			
(5) Have trouble breathing, or struggle to breathe?			

Have you ever…

	Yes	No	Not Sure
(6) Seen your child stop breathing during the night?			

Does your child…

	Yes	No	Not Sure
(7) Tend to breathe through the mouth during the day?			
(8) Have a dry mouth on waking up in the morning?			
(9) Occassionally wet the bed?			
(10) Wake up feeling unrefreshed in the morning?			
(11) Have a problem with sleepiness during the day?			

	Yes	No	Not Sure
(12) Has a teacher or other supervisor commented that your child appears sleepy during the day?			
(13) Is it hard to wake your child up in the morning?			
(14) Does your child wake up with headaches in the morning?			
(15) Did your child stop growing at a normal rate at any time since birth?			
(16) Is your child overweight?			

This child often…

	Yes	No	Not Sure
(17) Does not seem to listen when spoken to directly.			
(18) Has difficulty organizing tasks and activities.			
(19) Is easily distracted by extraneous stimuli.			
(20) Fidgets with hands or feet or squirms in seat.			
(21) Is "on the go" or act as if "driven by a motor."			
(22) Interrupts or intrudes on others (e.g. butts into conversations or games).			

Based on Chervin et al., Sleep Medicine, 2000.

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RESPONSE TO CRITIQUE:
PROPOSAL FOR SUPPORT ANCILLARY STUDY:
PRE-SCHOOL SLEEP-DISORDERED BREATHING

Anna Maria Hibbs, MD, MSCE
Case Western Reserve University, Rainbow Babies and Children's Hospital
July 15, 2009

We thank the protocol committee for their comments, which we responded to in detail below. Changes in the protocol are marked in the text in italics.

Review –
This proposal has the following specific aims:
(1) Describe the prevalence of SDB symptoms in 5-6 year old children born VLBW.
(2) Assess differences between the saturation arms of the SUPPORT study in SDB prevalence at 5-6 years of age.
(3) Determine whether infants with a higher % of desats below target are more likely to have SDB at age 5-6 years
(4) Determine whether previously identified risk factors for SDB in older cohorts are also risk factors for SDB in 5-6 year old VLBW children.

The methodology is as follows:
Study Design/ Definition of Population: This ancillary study will add a brief questionnaire to the planned 5-6 year follow-up assessment of the children in the SUPPORT trial.
Description of Intervention: A validated, one-page, 22-item sleep-questionnaire will be administered to the parent(s) that takes 10-15 minutes to complete.

Comments
I believe that this proposal is reasonable and will take advantage of the 6 yr follow-up.
I have a number of concerns
1. The rate of SDB quoted is for 8-11 yr olds – what is that rate that can be determined at 6 yrs?

Determining the true prevalence in the VLBW population at this age is one of the specific aims because previous studies of SDB in infants born preterm have focused on preterm infants (all birth weights) at school-age and VLBW infants in young adulthood.[1, 2] While the rate of SDB in VLBW infants at 6 years of is not specifically known, we do not expect it to be meaningfully lower than at 8 years, because the peak prevalence of childhood SDB is thought to occur at 2-8 years of age,[3] and the VLBW population is likely to have more comorbidities than the general preterm population. Thus, in our power calculations the 8 year prevalence in the general preterm population represents a conservative estimate.

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2. The questionnaire is brief – but there is a concern that the 6 yr exam etc may be long. Can this be administered during tracking at age 5 – will that change the outcomes? – this may enhance tracking and the questionnaire does not require a visit – could it be administered by phone?

We propose that it be administered by phone 1-6 weeks before the visit. Thus, the phone-call could both serve as a reminder/recruitment call, but also would be close enough to the study visit for anthropometric data such as BMI and Mallampati score to be relevant to the questionnaire results (see below).

3. Why have the investigators focused on the SpO2 values and not the need for intubation which can affect the airway. Thus CPAP or intubation may have a potential affect, and infants who required prolonged intubation may be at particular risk.

We agree that intubation and degree and duration of respiratory support will be important risk factors and/or potential confounders to assess as part of this study. In the Finnish study of young adults, there was no association between SDB and a history of mechanical ventilation. However, in the Cleveland Children's Sleep and Health Study (CCSHS), there was a non-significant suggestion that there may in fact be an association between degree of neonatal respiratory support and subsequent SDB; compared to infants with no respiratory support, the odds of SDB for children on oxygen or CPAP was 2.31 (0.23-23.30) and for infants with a history of intubation 3.74 (0.49-28.67). It may be that in the larger SUPPORT population, such an association would be identified, and certainly, just as with the SaO2 analysis, the SUPPORT trial would be an ideal population in which to address this question. The protocol has been modified to add this aim.

4. How do they propose to look at SpO2 values? Will they compare time below target, duration below 80% etc? This should be specified.

We propose using the percent of time with saturation less than 80%.

5. Is obesity/overweight a factor and will it be evaluated?

Obesity is a risk factor for SDB in children, although to a greater degree in post-pubertal patients. We propose using a BMI calculated at the study visit to adjust for obesity in the analyses if obesity is in fact associated with SDB in the SUPPORT population and in not equally distributed between randomized groups.

6. Could one add a quick oral examination to the 6 year exam – ie open your mouth and note the modified Mallampati score? (Mallampati, S. Ret al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J. 1985 Jul; 32(4):429-34.) This takes about 20 seconds or less.

We support the evaluation of the Mallampati score at the 6 year visit.

I would like to see the answers to the above queries before giving approval for this proposal.

Comments on proposal: "Pre-school Sleep-Disordered Breathing"

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General: Dr. Hibbs has submitted a very interesting proposal that would investigate an inadequately studied and potentially extremely important problem. Extended follow-up of at least part of the SUPPORT cohort to 6-7 years would provide a unique opportunity to study SDB in extremely preterm infants, strengthened further by the fact that these children are within the context of a RCT of neonatal respiratory interventions. From the proposal description, it appears that only limited time (~15 minutes) would be required to administer the appropriate questionnaire for this ancillary. However, a major concern is that the 6-7 year neurodevelopmental follow-up visit is already quite long (in fact, we are in the process of trying to streamline the visit substantially), so the addition of any further questionnaires must be carefully considered. The size and description of the subcohort to which this ancillary would be attached should also be clarified.

Please see the response to (2) above regarding moving the SDB questionnaire to a reminder call prior to the 6 year visit. This strategy has the potential of limiting any additional burden during the visit, adding a contact with the family prior to the visit which could boost compliance with follow-up, and still being close enough to the visit to make use of anthropometric data and other variables gathered at the visit.

Specific comments and questions:

Abstract/Statement of Problem

- Description of targeted extended follow-up subcohort: From my reading of the proposal, it appears that an assumption is made that the *entire* SUPPORT trial cohort will be followed at 6-7 years. This is not the case. Currently, only the Neuroimaging and Neurodevelopmental Outcomes Secondary to SUPPORT subcohort has been approved for extended follow-up. That subcohort is *expected to include ~530-550 survivors to discharge* at the close of the trial. I hope (and dare I say expect) that the Breathing Outcomes Secondary to SUPPORT subcohort will also receive approval for extended follow-up as well. Dr. Tim Stevens *expects ~750 survivors to discharge in that subcohort by the close of the trial.* The proposal should be revised to reflect this information, particularly the power/detectable difference calculations.
    - Do the authors envision this ancillary to be more appropriately attached to the Neuroimaging and Neurodevelopmental Outcomes extended follow-up, or to Breathing Outcomes extended follow-up (assuming it is funded)? There could be benefits to either – as described further below.

  We propose that this ancillary be linked to the breathing outcomes study to maximize sample size and to benefit from the availability of other important respiratory confounders and risk factors, such as exposure to cigarette smoke. The sample size calculations in the protocol have been modified to reflect an expected sample size of 750. This would represent the largest cohort assessing SDB in children born preterm to date.

- Age at follow-up: Throughout the proposal, extended follow-up is described as "5-6 year follow-up". In fact, the approved Neuroimaging and Neurodevelopmental Outcomes extended follow-up and the proposed Breathing Outcomes extended follow-up will occur at **6-7 years**.

  The protocol has been revised to reflect follow-up at 6-7 years.

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- Risk factors for SDB: Are any data available that would relate to hypotheses regarding specific *neonatal neuroimaging findings and risk for SDB?* Since the patients enrolled in the Neuroimaging and Neurodevelopmental Outcomes group will have specifically-timed cranial US and near term brain MRIs, all interpreted by central reader neuroradiologists, this would provide a unique chance to test such a hypothesis (assuming data support the proposal of such a hypothesis).

  For the reasons described above, we propose linking this ancillary study to the breathing outcomes study. However, secondary exploratory analyses could be performed on the subset of patients enrolled in both protocols. While the current literature does not support a link between neonatal ultrasound abnormalities and subsequent SDB, near-term MRI findings have not been assessed. In addition there is some evidence that SDB is associated with concurrent MRI changes, although many authors suggest that the SDB causes the neuroimaging changes. Hoewever, no one specific MRI abnormality is consistently reported. Using magnetic resonance spectroscopy (MRSI) Hallbower showed differences in hippocampal neuronal metabolism in children with SDB[4]. In addition, in adults, there is some mixed data suggesting a variety of detectable brain difference in the MRI's of patients with SDB, including lower fractional anisotrophy on diffusion tensor imaging, hippocampal atrophy, and other lesions.[5, 6] In addition, in the CCSHS, children born preterm were found to be more vulnerable to the neurocognitive effects of SDB; childhood neuroimaging was not done in this cohort.[7] Thus, an exploratory analysis of the subset of children enrolled in both follow-up protocols would address: (1) are neonatal MRI abnormalities associated with increased risk of childhood SDB (2) is SDB in childhood associated with concurrent MRI abnormalities? These exploratory analyses would require no new data collection. In the revised protocol, power calculations for this analysis are based on a conservative estimate of 350 infants enrolled in both the MRI follow-up and the Breathing Outcomes follow-up.

- *Hypotheses/Specific Aims*
- Patient description: It would probably be a good idea to be quite specific about the patients to be studied – in other words, instead of "children born VLBW", a more complete description based on SUPPORT entry criteria would be useful here.

  A brief summary of the SUPPORT entry criteria has been added to the revised protocol.

- 3rd hypothesis: Is there a specific oxygen saturation floor, or % of time spent below a proposed lower limit saturation that relates to this hypothesis?

  We propose to use time spent at a saturation <80%.

- 4th hypothesis: I do not believe the GDB NG02 captures information specifically on maternal *pre-eclampsia* (although maternal hypertension during and prior to pregnancy is queried), nor does it capture maternal smoking data. However, assuming the Breathing Outcomes extended follow-up is funded, there will be quite a bit of data regarding smoking exposure captured for that subcohort.

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Maternal hypertension during pregnancy can be used in lieu of the pre-eclampsia variable. Smoking exposure at the 6-7 year visit is now proposed to measure smoking exposure.

- As noted above, hypotheses related to neuroimaging findings (particularly by MRI) would be interesting and appropriate to the Neuroimaging and Neurodevelopmental Outcomes cohort if supported by previous data.

  Please see response above.

- *Methods/Design/Statistical considerations*
- SRBD scale:
  - Is this questionnaire available/validated in Spanish?

    To our knowledge it is not available in Spanish. It is straight-forward and could be translated easily. A copy of the questions are appended to the end of the protocol.

  - The authors suggest that the questionnaire may be streamlined to remove attention deficit/hyperactivity component. We will be administering the attention/hyperactivity component of the Conners Rating Scale as well as the Strengths and Difficulties Questionnaire at 6-7 years, so we will have substantial information on attention and hyperactivity. It would be fantastic if we could save some time by cutting this domain of the SRBD questionnaire, and thus overlap could be avoided to reduce parental frustration. However, has the SRBD scale been validated *without* this component? If this domain is removed, could the proposed analyses be carried out as described (i.e., primary outcome defined by average score $\geq$0.33 on the SRBD scale)?

    We propose retaining the attention/hyperactivity component of the scale for the reasons mentioned and administering the scale by telephone as recommended above.

- Sample size: As noted previously, the entire SUPPORT cohort will not be followed to 6-7 years. The Neuroimaging and Neurodevelopmental Outcomes cohort is expected to have ~530-550 survivors to discharge by the close of SUPPORT. Estimating ~25% loss to follow-up, 400-420 would be seen in follow-up at 6-7 years. The SDB ancillary proposal estimates are based on the *total* SUPPORT cohort patient numbers (i.e., 1021 survivors to discharge, ~817 patients to extended follow-up). The Breathing Outcomes secondary cohort will be larger (~750 survivors to discharge by close of SUPPORT). The detectable difference calculations should be revised to reflect this information, and to determine if the true available sample size at 6-7 years would allow for detection of reasonable SDB difference from the general population estimates.

  We have revised our sample size estimates in the protocol to reflect the 750 infants expected in the breathing outcomes cohort.

The sample size they assume (n = 817) is clearly unattainable, because the neuroimaging follow up is predicated on a sample size of 350 and the pulmonary follow

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up assumes a sample size of 384 at 6-7 years. So, they need to revisit those calculations and see if the study is still doable with the reduced sample size. Also, both these FU samples may not be representative of the trial population in general. The analysis plan needs to give some thought to that issue.

See above. In addition, we have added a comparison of characteristics of the infant followed versus not followed to the protocol.

Follow up is being done at 6-7 years, not 5-6 years. The neuroimaging cohort will have 350-450 children seen, not 817. A recent concept for breathing outcomes follow up was approved by the steering committee, so more children may be seen pending approvals.

The protocol has been revised to reflect follow-up at 6-7 years.

Is the rate of SDB higher in infants 24-27 6/7 weeks than in preterm infants in general? If so, less children will be needed for inclusion in the study. More detail in the analysis section is needed.

Data from the Cleveland and Finnish cohorts would suggest that there is NOT a higher rate in the smallest or most immature infants; simply being premature or VLBW is a risk factor with no apparent gradation by size or immaturity. The sample size calculations have been revised to target the breathing outcomes population as described above.

Is there a form or questionnaire that the committee can review to assess time of the interview?

A questionnaire is attached at the end of the protocol.

There is need for a budget for this study.

A budget is included.

References

1. Paavonen EJ, Strang-Karlsson S, Raikkonen K, et al. Very low birth weight increases risk for sleep-disordered breathing in young adulthood: the Helsinki Study of Very Low Birth Weight Adults. Pediatrics 2007;120:778-84.
2. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003;142:383-9.
3. Au CT, Li AM. Obstructive sleep breathing disorders. Pediatr Clin North Am 2009;56:243-59, xii.
4. Halbower AC, Degaonkar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 2006;3:e301.

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5. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep 2008;31:967-77.
6. Zimmerman ME, Aloia MS. A review of neuroimaging in obstructive sleep apnea. J Clin Sleep Med 2006;2:461-71.
7. Emancipator JL, Storfer-Isser A, Taylor HG, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. Arch Pediatr Adolesc Med 2006;160:203-10.

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From: Rich, Wade
To: Wally Carlo, M.D.; chudson@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Manuscript for Review 7/1/2009 - Antenatal Consent Paper
Date: Thursday, July 16, 2009 10:46:44 AM

Hi Wally,
Neither Marie nor I were able to interpret this statement. The non-enrolled infants were taken from eligible GDB infants, and not all of them even have Ante. Data. Can you
Ask the reviewer to try and clarify what they want, or if you understand, please help us ?
Thanks
wade

" I did have a question about the statement of infants who were enrolled in SUPPORT vs. the non-enrolled being significantly different. Especially about the discussion of antenatal steroid use—were authors able to characterize reason for not giving steroids? Were these all consented or some consented and some not? Would be interesting to see if there were more consents in the group who were consented despite enrollment or delivery in the window. "

wade

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 16, 2009 5:51 AM
To: Rich, Wade; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Cassandra Hudson
Subject: FW: Manuscript for Review 7/1/2009 - Antenatal Consent Paper

Hi Wade:

Enclosed is an excellent review.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
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Cell: 205 266 (b) (6)

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: SUPPORT SUMMARY
Date: Thursday, July 16, 2009 9:58:00 AM
Attachments: 2010 ATS Noon Proposal SUPPORT.DOC

Rose and Neil:

I have made tracked changes.

It is excellent.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 16, 2009 8:07 AM
To: nfiner@ucsd.edu; Wally Carlo, M.D.
Subject: Fw: SUPPORT SUMMARY

Please send comments
Rosemary D. Higgins, MD
Program Scientist

From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Jul 16 08:16:27 2009
Subject: RE: SUPPORT SUMMARY

Rose,
This is my draft, which I welcome you to edit. There are word limits you will notice.
Also attached is what I submitted for last year's iNO session for comparison.
I am attending a PPG review almost all day today, so after editing, I am fine for you to circulate to Neil and Wally (just cc me, so I know when we have the feedback and hopefully I can get this to Jim Kiley (Div Lung Diseases director) tomorrow.
The speakers (moderators) don't have to be committed yet.
If you think other literature should be here for the ATS committee to understand the field that are different than the 3 I suggested—feel free to replace.
Also, please fill in the pulse ox target ranges.

cb

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Carol J. Blaisdell, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 15, 2009 2:55 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: SUPPORT SUMMARY

Carol
This may e of help – the SUPPORT summary available on our website.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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This proposal has not been submitted.

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ATS 2010 * New Orleans Outside Organization Session Proposal ID:

Submitted By:	james p kiley Ph.D.	**Phone Number:**	3014350233
Institution:	Division of Lung Diseases/ National	**Fax:**	3014803547
	Heart, Lung, and Blood Institute/		
	National Institutes of Health/Dept.		
	of Health and Human Services		
E-mail Address:	kileyj@nhlbi.nih.gov		

Session Information

Title Outcomes from the NHLBI-NICHD SUPPORT Trial: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight (ELBW) Infants

Target Audience *e.g. For providers of lung health? Specific Assemblies? Serving a specific patient group or multiple groups? Will your learners have clinical, research, administrative responsibilities? Do they need to learn about areas of medicine outside of their specialty?*

pulmonologists/neonatologists/pediatricians

Should attendees have specific expertise to benefit from this session? ☒ yes (clinical) ☐ no

Session Summary Include a brief summary of the course content, from the perspective of the learner, which runs no longer than 75 words.

Extremely low birth weight (ELBW) premature neonates suffer from higher~~increased~~ rates of ~~morbidity and~~ mortality and increasing rates of pulmonary morbidity compared to term newborns. Advances in therapy for the premature ~~have~~ suggested that mode of ventilation and oxygen toxicity increase risk of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). Results will be presented from the NHLBI / NICHD SUPPORT trial -- a prospective, randomized, factorial 2x2 design large multi-center trial that tested early CPAP versus standard~~and~~ mechanical ventilation management with a low or high pulse oximetry target on outcomes of BPD and ROP.

Have you served as faculty for a similar session before? ☒ yes ☐ no

Organization Name National Heart, Lung, and Blood Institute and National Institute of Child Health, NIH

Statement of Clinical/Scientific Importance Please state in 250 words or less the educational need for this session to be presented to ATS International Conference attendees. Identify the methods you used in determining this need by checking appropriate boxes below, rather than stating them in narrative.

1 What is that difference between current and optimal practice you wish to address with education? (This is called the professional practice gap.)
2 In order to narrow or eliminate the gap will your offering increase knowledge, competence (knowing how to do something), performance in work or practice or patient health/quality of life?

1) Current practice in neonatal intensive care units (NICU) is variable on the use of continuous positive airway pressure (CPAP) as an alternative to conventional ventilation, which permits early use of surfactant (a known beneficial treatment to prevent respiratory distress syndrome and BPD). In

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addition, many clinicians in many NICUs have practices that permit oxygen saturation targets in the mid 80% range to reduce the incidence of ROP.

2) The SUPPORT trial was designed to close the gap on knowledge of the most effective strategies for the support of breathing and oxygenation in the very preterm infant. The effect of the alternative mode of ventilation (CPAP) without early use of surfactant combined with low (85-89%—) vs. high (91-95%—) pulse oximetry management has not previously been studied in a randomized fashion. Neonatal Network investigators will present the results of the SUPPORT trial and moderators will lead a discussion of the evidence, which could inform clinical practice for the ELBW infant. Primary outcomes of BPD and ROP will be presented.

Please cite 2 or 3 resources or references that could be reviewed by the Program Committee as evidence of need, if requested.

te Pas AB, Spaans VM, Rijken M, Morley CJ, Walther FJ Early nasal continuous positive airway pressure and low threshold for intubation in very preterm infants. *Acta Paediatr.* 2008 Aug;97(8):1049-54

Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH; AVIOx Study Group. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics.* 2006 Oct;118(4):1574-82

Finer N, Leone T. Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. *Pediatr Res.* 2009 Apr;65(4):375-80

What sources did you use to assess the needs of this target audience? Check all the sources that apply.

- ☐ Requests from ATS members/similar learners
- ☐ Previous course evaluation asking for suggestions
- ☐ Survey of target audience (requesting content)
- ☐ Self-assessment tests (e.g. pre-test, post test, case vignettes in surveys)
- ☐ Faculty perception
- ☐ Advice from authorities in the field
- ☐ This is a follow-up at a higher level to a previous course
- ☐ Review of literature
- ☒ New medical findings
- ☐ New guidelines
- ☐ Quality improvement data
- ☐ Formal needs assessment(s) by scholarly investigators
- ☐ Other

Can these data be applied to learners at the International Conference? ☒ yes ☐ no

Objectives Please provide three learning objectives below:

Your objectives should focus on closing the gap/solving the problem you identified under the Statement of Clinical/Scientific Importance. E.g. what will the learner be able to do/do better after attending your session? You may begin some of your objectives with the following: "will be able

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to describe"; "will learn new findings about..."; "will appreciate the importance of...". At least one of your objectives should state how the learner will be able to apply new knowledge competence or performance/skill to his practice or work or improve quality of life or health of the patient. Eg. "will be better able to diagnose..."; "more appropriately refer..."; "refer earlier..."; "will have new strategies to manage the care of..."; "will integrate new treatment options in discussing xxx with the patient..."; "will be able to improve the quality of life/health status of his patients by xxx."

At the conclusion of this session, the learner will be able to:

1. To learn the impact of early CPAP on BPD and ROP in the SUPPORT trial
2. To learn the effect of high vs. low pulse oximetry targets on risk of BPD and ROP in the ELBW infant
3. Understand the interaction of mode of ventilation and target pulse oximetry on outcomes of BPD and ROP in ELBW infants.

Initial Disclosure of Faculty Conflicts of Interest

ATS International Conference requirements for disclosure and management of conflict of interest are based upon the ATS

Policy on Management of Conflict of Interest and **Policy on Tobacco Relationships.** Session proponents must complete the questions below as an initial disclosure. If the session is approved, session organizers, chairs and presenters will complete a detailed disclosure form and appropriate ATS oversight committees will review the disclosures as part of their oversight of sessions.

Please note:

- Many individuals have competing interests that may cause conflicts of interest. A COI depends on the situation and not on the character or actions of the individual. Examples of potential conflicts include personal financial relationships with commercial entities, or government or foundation funders, that are relevant to the session, including employment by a commercial entity; consultancy(ies); Board or Advisory Board; lecture fees; service as an expert witness; research grants; patents received or pending; royalties; and stock ownership or options (excluding mutual funds unless a sector fund concentrated in an industry[ies] relevant to the activity).
- The ATS "Policy on Tobacco Relationships" requires that individuals with a current tobacco industry relationship (or one in existence between now and the conclusion of the 2010 International Conference) not serve as a session planner (organizer), chair or presenter. (If limited to personal holdings of tobacco stocks or options, divestiture of such holdings a minimum of 30 days before the conference restores eligibility. See the policy for details.)
- Disclosure of a real or potential COI will not automatically invalidate a session proposal.

Session Proposer

1. Do you, as the proposer, have a personal financial interest(s) in a commercial entity (such as a pharmaceutical company or medical device manufacturer) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

2. Do you, as the proposer, have a personal financial interest(s) in a non-commercial entity (such as support from a government source or foundation or other non-profit source) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

3. Do you, as the proposer, have knowledge of your institution or employer having a significant financial relationship with a commercial entity that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

4. Do you, as the proposer, have a relationship with a tobacco entity at present, or may within the twelve months prior to the conference?

   ☒No ☐Yes

Proposed Faculty

1. To your knowledge, does any other member of the proposed faculty (presenters) have a personal financial interest(s) in a commercial entity (such as a pharmaceutical company or medical device manufacturer) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

   ☒No ☐Yes

2. To your knowledge, does any other member of the proposed faculty (presenters) have a personal financial interest(s) in a non-commercial entity (such as support from a government source or foundation or other non-profit source) that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

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☒No ☐Yes

3. To your knowledge, does the institution or employer of any other member of the proposed faculty (presenters) have a significant financial relationship with a commercial entity that might be perceived as a real or potential conflict of interest (COI) relevant to the subject matter of this proposal?

☒No ☐Yes

4. To your knowledge, does any other member of the proposed faculty (presenters) have a relationship with a tobacco entity at present, or may within the twelve months prior to the conference?

☒No ☐Yes

Topics and Faculty **Proposed Presenters and Topics**

Add Faculty (include self)

1. First Name Carol
Middle Name J.
Last Name Blaisdell
Suffix
Degrees M.D.
Institution National Heart Lung and Blood Institute, NIH
E-mail blaisdellcj@nhlbi.nih.gov
☐Chair ☒Cochair ☐ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

2. First Name Rosemary
Middle Name
Last Name Higgins
Suffix
Degrees M.D.
Institution National Institute of Child Health, NIH
E-mail higginsr@mail.nih.gov
☐Chair ☒Cochair ☐ none

☒ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

3. First Name Neil
Middle Name N.
Last Name Finer
Suffix
Degrees M.D.
Institution University of California, San Diego
E-mail nfiner@ucsd.edu
☐Chair ☐Cochair ☐ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

4. First Name Waldemar
Middle Name A.
Last Name Carlo
Suffix
Degrees M.D.
Institution University of Alabama at Birmingham
E-mail wcarlo@peds.uab.edu
☐Chair ☐Cochair ☒ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

5. First Name Dale
Middle Name
Last Name Phelps
Suffix
Degrees
Institution University of Rochester
E-mail dale_phelps@urmc.rochester.edu
☐Chair ☐Cochair ☒ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

6. First Name Colin
Middle Name
Last Name Morley
Suffix
Degrees M.D.
Institution
E-mail
☐Chair ☐Cochair ☒ none

☐ Check here to confirm that the proposed chairperson(s) has knowledge of the submission of this proposal and has agreed to serve as chair if the session is approved for presentation.

Add Topic For each talk topic, assign a presenter listed above. You may enter up to 6 talks. Enter the length of time in minutes only

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1. Presenter Rose Higgins
   Proposed Topic: Overview of SUPPORT
   Description: an overview of the NICHD network and brief introduction of the SUPPORT trial
   Length of Time (minutes) 5 minutes

2. Presenter Neil Finer
   Proposed Topic: CPAP vs. Intubation with Surfactant
   Description: Design of the study and primary outcomes related to mode of ventilator support
   Length of Time (minutes) 15 minutes

3. Presenter Waldemar Carlo
   Proposed Topic: Pulse oximetry, outcomes from high vs low targets
   Description: Design of the high vs. low pulse oximetry management strategy, and outcomes of BPD and ROP will be presented
   Length of Time (minutes) 15

4. Presenter Dale Phelps
   Proposed Topic: Moderator/Discussant
   Description Discussion of the study design and outcomes presented and facilitation of audience participation
   Length of Time (minutes) 5 minutes

5. Presenter Colin Morley
   Proposed Topic: Moderator/Discussant
   Description Discussion of the study design and outcomes presented and facilitation of audience participation
   Length of Time (minutes) 5 minutes

6. Presenter
   Proposed Topic
   Description
   Length of Time (minutes)

The ATS reserves the right to seek corporate support for all programs accepted for presentation at the International Conference.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: ATS conference SUPPORT trial
Date: Wednesday, July 15, 2009 2:17:43 PM

I can be on the call.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 15, 2009 2:12 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ATS conference SUPPORT trial

Neil can make it. I have also asked Marie Gantz and Abhik Das from RTI to join.

2:30 PM –
Call 1-866-675(b) (6) with passocde (b) (6)

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, July 15, 2009 2:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Subject: RE: ATS conference SUPPORT trial

Can we start with a conversation at 2:30 (eastern) today?
Neil hasn't had a chance to respond yet, but I am on a tight timeline for drafting something (due this Friday). Happy to follow up with Neil if he is unable to join today.
Rose, please send us some numbers to use.

Carol

Carol J. Blaisdell, M.D.
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Lung Developmental Biology and
Pediatric Pulmonary Diseases
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 15, 2009 1:39 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Subject: RE: ATS conference SUPPORT trial

I am free after 2:30 PM ET – I have a call in number we can use. This is a great opportunity for the NRN.

Rose

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, July 15, 2009 1:38 PM
To: 'Nfiner@ucsd.edu'; 'wacarlo@uab.edu'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ATS conference SUPPORT trial

Dear Neil and Wally,
Rose let me know that you were interested in submitting abstracts to PAS for the SUPPORT trial.

NHLBI has the opportunity to recommend for noon conferences (1 hour) the clinical trials that we (and in this case NICHD) support at the American Thoracic Society meeting each year.

I would like to work with you to develop a plan to present SUPPORT for the ATS attendees as well, using the NHLBI noon conference format as a mechanism for submission.

Please let me know if you might have time later today/tomorrow to discuss.
Attached is the format that ATS uses for submitting session proposals.

Carol

Carol J. Blaisdell, M.D.
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Pediatric Pulmonary Diseases
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(301) 435-0222 phone
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ATS conference SUPPORT trial
Date: Wednesday, July 15, 2009 2:16:05 PM

I will need to get off the call by 11:50
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 15, 2009 11:12 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Finer, Neil; wacarlo@uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ATS conference SUPPORT trial

Neil can make it. I have also asked Marie Gantz and Abhik Das from RTI to join.

2:30 PM –
Call 1-866-675-(b) (6) with passocde (b) (6)

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, July 15, 2009 2:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Subject: RE: ATS conference SUPPORT trial

Can we start with a conversation at 2:30 (eastern) today?
Neil hasn't had a chance to respond yet, but I am on a tight timeline for drafting something (due this Friday). Happy to follow up with Neil if he is unable to join today.
Rose, please send us some numbers to use.

Carol

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Pediatric Pulmonary Diseases
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(301) 480-3451 fax
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 15, 2009 1:39 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Nfiner@ucsd.edu; wacarlo@uab.edu
Subject: RE: ATS conference SUPPORT trial

I am free after 2:30 PM ET – I have a call in number we can use. This is a great opportunity for the NRN.

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Rose

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, July 15, 2009 1:38 PM
To: 'Nfiner@ucsd.edu'; 'wacarlo@uab.edu'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ATS conference SUPPORT trial

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From:	Cassandra Hudson
To:	wrich@ucsd.edu
Cc:	Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject:	FW: Manuscript for Review 7/1/2009 - Antenatal Consent Paper
Date:	Wednesday, July 15, 2009 8:12:00 AM
Attachments:	ANS.manuscript.review.doc ANS consent review.doc

Dear Dr. Wade,
Attached is the first review of your ANS paper.

Thanks,
Cassandra Hudson
(office of Dr. Wally Carlo)

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

Wade Rich BSHS, RRT[1], Kathy Auten MSHS[2], Marie Gantz PhD[3], Ellen Hale RN,BS[4], Angelita Hensman RNC[5], Nancy Newman BA, RN[6], and Neil N Finer, MD[1] on behalf of the NICHD Neonatal Research Network

[1] UCSD Medical Center, San Diego, CA; [2]Duke University, Durham NC, [3]Research Triangle Institute, RTP, NC, [4]Emory University, Atlanta GA, [5]Women' and Infant's Hospital, Providence, RI[6]Case Western University, Cleveland OH

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Keywords: Informed Consent, Antenatal, Neonatal

The authors have no financial disclosures or conflicts of interest.

ABSTRACT

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Objective:

The purpose of t~~T~~his study was designed was to quantify the time ~~and~~ effort, and success involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial, ~~and to better predict the time required for recruitment into~~ a complex interventional trial requiring antenatal consent.

Design/Methods: I

~~A data form was designed to obtain~~ Information about eligible mothers who were available and approached at each center was collected, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled in the trial. ~~Infants born at Network centers who delivered in the SUPPORT (24 0/7 to 27 6/7 wk GA)~~Eligible, non-enrolled infants ~~were~~ entered into the NRN Generic Database were identified to allow comparison of enrolled and non-enrolled infants. ~~These data were used to identify infants who were eligible but not approached or enrolled.~~

Results

2828 women were identified at 18 NRN sites ~~collaborating units as being~~ to be at risk for premature delivery ~~at 24 to 27 6/7 wks GA~~ between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities (x%), active labor (Y%) and language barriers (Z%). A study coordinator~~/research nurse made 75% of all approaches~~ approached 75% of all mothers . For 77% of those approached, ~~consent was attempted~~ < 3 visits were made to complete the consent process~~times~~. (~~Overall~~ mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of ~~those~~ mothers approached had~~were identified as having~~ been previously approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 (XX%) gave consent. Five hundred seventy-eight of those consented delivered 655

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infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window ~~were not enrolled i.e., consent was given but~~ did not receive the study-prescribed interventions ~~was not undertaken~~. Only 19% of screened women delivered infants subsequently enrolled in the study. ~~There was a significant relationship between performing a neonatal consult and obtaining consent~~ Mothers who received a neonatal consult were more likely to give consent ($p<.0001$). Centers that were ~~also~~ NICHD Maternal Fetal Medicine network centers had ~~enrolled at~~ a higher consent rate and were more likely to obtain consent in ~~use~~ < 30 minutes ~~to obtain consent. A significantly higher proportion of infants who delivered in the study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled.~~ Infants not enrolled in the SUPPORT trial had a lower rate of ANS use (3.8 vs. 15.7~~15.7 vs. 3.8~~% $p<.0001$) and this~~. The~~ difference was more significant in those not approached when compared to those approached~~in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women~~ (20.3 ~~3.4~~ vs. 3.4~~20.3~~%, $p<.0001$).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, ≥~~more than~~ 5 women were identified as likely to deliver a baby in the GA window for each one who delivered an infant enrolled in the trial. Extrapolating these data ~~to the entire SUPPORT trial~~ suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the SUPPORT trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

~~The process of~~ Informed consent ~~was established to~~ ensures that subjects enrolled in research trials are~~were~~ appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represent~~ed~~ an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery ~~to provide consent for their infant(s)~~.

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Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and ~~some pre-calculated screening time~~some time allotted for screening. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are

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actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

~~Early enrollment~~ Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent numbers~~rates~~. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the second~~last~~ half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was planned~~expected~~.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff collected~~self-reported~~ study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for

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antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were ~~approached for SUPPORT~~ approached were asked if they were approached for participation in any other studies ~~either~~ for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the ~~entire~~ eligible NRN~~etwork~~ population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. Eligible but non-enrolled infants had information collected on ~~This information included whether~~ prenatal care ~~was obtained~~, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

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We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and were otherwise eligible for participation in the SUPPORT trial. Two ~~additional~~ NRN centers did not participate in the antenatal consent trial and 4 participating centers~~who did participate~~ did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were ~~informed that they could~~ told to stop collecting data. All data collected by participating centers have been included in this analysis. A~~Results of an a~~nalysis using only the first 50 women from the centers that over-enrolled were not significantly different. S~~Data for s~~creening, enrollment and consent numbers by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. M~~Reasons m~~others were considered unable to give consent when in~~included being in~~ active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not

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significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 (XX%) gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. ~~There was a significant relationship between performing a neonatal consult and obtaining~~ Mothers receiving a neonatal consult were more likely to consent (p <.0001), but consent was ~~only~~ obtained during the consult in only 12% ~~of the time~~. Centers that were ~~also~~ NICHD Maternal Fetal Medicine network centers enrolled at a higher rate (higher consent % or just larger numbers of infants approached?) and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision. (Did an MD making the first approach for consent have any influence on the success rate?)

Infants of non-approached and approached mothers were different in several important ways (Table 2). Infants of approached mothers were more likely to be non-Hispanic white (p<0.0001); ~~the mothers were more likely to be~~ older (p=0.0210) and to have a high school education (p<0.0001), medical insurance (p<0.0001), and at least one PNC visit (p<0.0001). (The N is large enough that p values of this magnitude for relatively small differences are not that surprising. Other than the clearly large and important difference in antenatal steroids, are any of these other differences thought to be clinically significant as well as statistically significant?) A significantly higher proportion of eligible non-enrolled infants not approached~~born in the study window whose mothers were not approached for SUPPORT~~ had no exposure to antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

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Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance (p=0.0011) and to have received prenatal care (p=0.0039), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, p<0.0001) (Table 3).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain antenatal consent from parents for the enrollment of their u~~premature~~nborn infants ~~who at the time of the consent were not yet born~~. Our results reveal that 5 families needed to be identified and screened for every one ~~that had an~~ infant successfully enrolled. Only 47% of women c~~from whom consent was obtained~~ onsented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a -maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus,

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we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which c~~-did keep-~~ollected data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment

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occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[12] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[13] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[14]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point

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toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

O~~The bias in o~~ur analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population ~~studied~~enrolled as a result of antenatal consent -may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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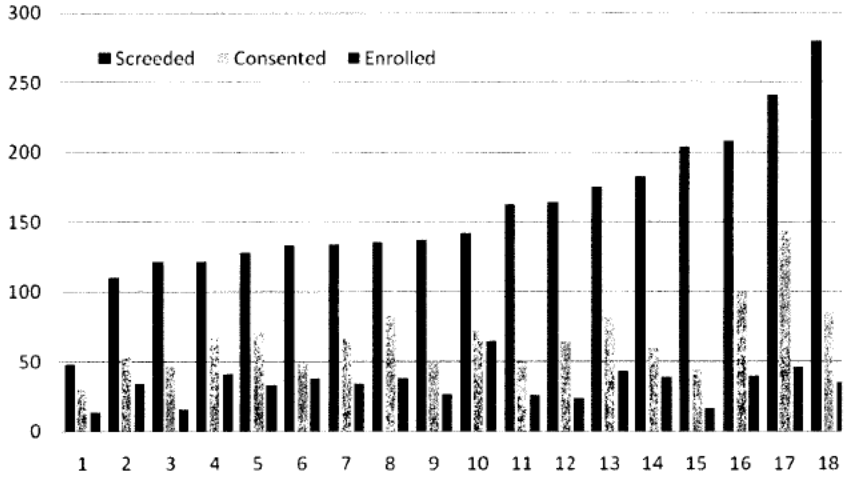

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 1. Reasons for not approaching mothers for consent.

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505

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≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039
No Antenatal Steroids	3.8	15.7	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

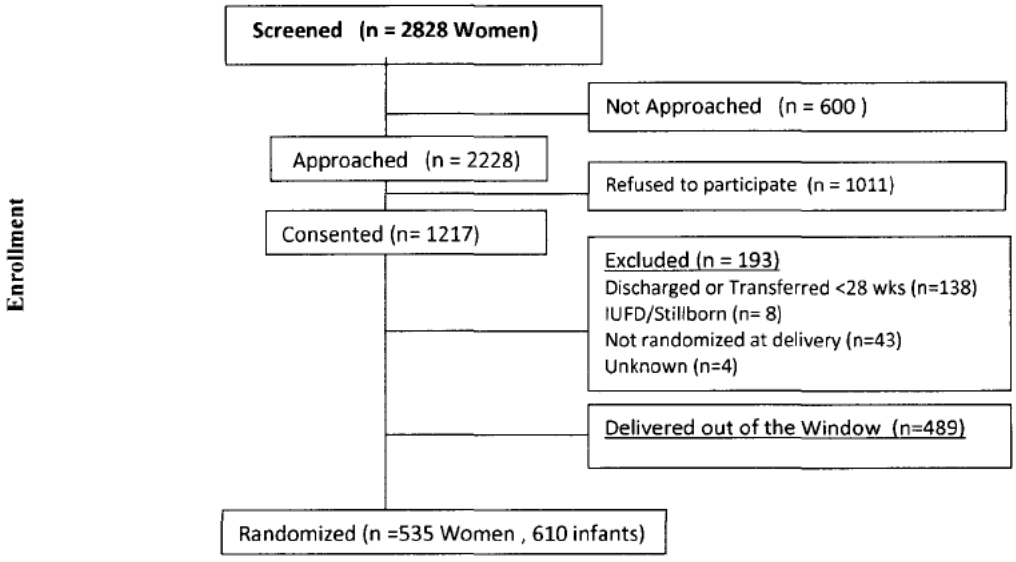

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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July 13, 2009

Dear Wally and Wade,

Thank you for the opportunity to review this manuscript, which provides very useful information regarding the antenatal consent process for clinical researchers. The effect of antenatal consent on the demographics of the enrolled infants is an important finding.

My overall comments are:

1. The majority of my comments are minor (wording suggestions included in manuscript with track changes).
2. I suggest placing each figure and table on a separate page with the title at the top.
3. The format for the references should be consistent and based on the specifications of the journal it will be submitted to.
4. Were there any center differences in overall consent or any of the other variables you investigated?
5. The fact that infants with less ANS exposure, prenatal care, and insurance were not enrolled is very important and strongly supports the need for waiver of consent for this type of study.
6. Who were the 2nd and 3rd most common people to approach for consent?
7. Did consent rates differ significantly based on who was obtaining consent?
8. Figure 1, "screeded" change to "screened".
9. Figure 2, instead of "night, weekend holiday" I suggest Study staff unavailable".
10. Table 3, headings could be "Enrolled infants" and "non-enrolled infants".

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From: Diana Vasil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, July 14, 2009 4:26:58 PM

Hi Rose,

We have supplied the missing data or corrected information from the items sent. We will be transmitting for your update.

Thanks,
Diane

Diana M. Vasil RNC-NIC
UT-Southwestern Medical Center
Dept. Of Pediatrics
5323 Harry Hines Blvd.
Dallas, TX. 75390-9063
ph. 214-648-3789
fax 214-648-2481

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 7/13/2009 1:30 PM >>>

Hi,

We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

Thanks for all the hard work!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

CENTER

NETWORK

BPD_message

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4

(b) (6)

Infant has been discharged and was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is not entered.

4

(b) (6)

Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Hensman, Angelita
To: Higgins, Rosemary (NIH/NICHD) [E]; Laptook, Abbot; Vohr, Betty; Ventura, Suzy
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, July 14, 2009 9:28:21 AM

Per the ophthalmologist on 6/26/08 "eyes will never mature". We will recheck with mom at follow up when the baby comes in on [redacted].

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 13, 2009 2:46 PM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Ventura, Suzy
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

AMAZING GIVEN YOUR TERRIFIC RECRUITMENT!!!

Thanks for all the hard work!!!
Rose

CENTER	NETWORK	ROP_message
14	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, July 13, 2009 3:43:36 PM

Rose:

Thanks always for the positive tone of your reminders. It is encouraging that you recognize so much our nurses efforts.

I will miss these when we finish SUPPORT ☺

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 26(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 13, 2009 1:48 PM
To: Waldemar A Carlo; Monica Collins; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

This is fabulous given your outstanding recruitment!!!!

Thanks for all the hard work!!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16	(b) (6) 1	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, July 13, 2009 3:40:16 PM

Still zone two regressing. Oh, that it were zone 3...

wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 13, 2009 12:32 PM
To: Rich, Wade
Subject: RE: SUPPORT

Do you have 2 exams with vessels in zone 3?

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Monday, July 13, 2009 3:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

We have 13 eye exams for this baby, still not final. Will upload later today.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 13, 2009 12:08 PM
To: Finer, Neil; Rich, Wade
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

Thanks for all the hard work!!!
Rose

CENTER	NETWORK	ROP_message
22	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Monday, July 13, 2009 3:19:39 PM

will check.
ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

07/13/2009 03:09 PM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, <Kimberley.fisher@duke.edu>, <gloria.siaw@duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

Thanks for all the hard work!!!
Rose

CENTER NETWORK ROP_message		
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER NETWORK FU_message		
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

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From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Monday, July 13, 2009 3:10:15 PM
Importance: High

Hi,
We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.

Thanks for all the hard work!!!
Rose

CENTER	NETWORK	FU_message
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu; nancy newman; Gantz, Marie
Subject: Re: SUPPORT OUTCOMES
Date: Monday, July 13, 2009 3:03:24 PM

ANOTHER appt. 7/16/09.

On Mon, Jul 13, 2009 at 2:28 PM, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov> wrote:

> Hi,
>
> We are very close to having the majority of SUPPORT outcomes. Please let us know how you are doing. We are missing the following items based on last week's DMS entry.
>
> This is incredible given your recruitment – I know you are trying to get this information!!!
>
> Thanks for all the hard work!!!
> Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Friday, July 10, 2009 4:47:53 PM
Attachments: Infants with missing outcomes 07-10-09.xls

Attached is a list of the SUPPORT infants who are missing outcomes this week.

I am still working on a complete list of BPD queries. I have been working on them for over a week but they are not ready to go out yet and I only want to bother the centers once with this. I will keep you updated on my progress next week.

I also wanted to let you know that our final N for SUPPORT will be 1316 instead of 1317. One of the centers had apparently entered data for a stillborn baby; the twin was enrolled and both infants were mistakenly keyed for SUPPORT instead of just the one that was a live birth. Data for the stillbirth has now been removed from the SUPPORT and GDB files.

Thanks, and have a good weekend.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
12		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Das, Abhik
Subject: RE: BPD and ROP outcomes for SUPPORT
Date: Tuesday, July 07, 2009 2:24:26 PM

Hi Rose
My concern is that we don't want to see a difference between the groups – I understand that the overall rate is lower using the Physiologic.
Lets hope for similar trends
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 07, 2009 7:05 AM
To: Gantz, Marie; Finer, Neil
Cc: Das, Abhik
Subject: RE: BPD and ROP outcomes for SUPPORT

One more thing about BPD – less children had BPD by the physiologic definition in Michele's paper than by "oxygen use at 36 weeks" when first described, so, in fact, we may see a difference. I have attached the original paper (35% by oxygen definition, 25% by physiologic def)

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, July 07, 2009 9:43 AM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: BPD and ROP outcomes for SUPPORT

Thanks, Neil. I understand what you are saying about the two definitions of BPD. I think it makes sense to look at both once we have the final data.

With respect to ROP, each infant with missing ROP is only listed in one of the 6 categories in the output I sent. There are a total of 137 infants with missing ROP, as seen on the first page. For the 113 infants who are older than 55 weeks PMA, their age and status at last exam, current PMA, and status of FU window are listed on the following pages.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, July 06, 2009 7:56 PM
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik

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Subject: RE: BPD and ROP outcomes for SUPPORT

Hi Marie
Thanks for the data. I know that the primary is the Physiologic definition. I am trying to get a handle on the gross results – and we will report the BPD by oxygen at 36 weeks as well as that is what most centers use – certainly all international ones. In addition by our own data we did not do the withdrawal as required and thus we are using a definition for these infants that no one else uses or understands. We will ultimately have to make a decision as to their diagnoses of BPD and they will not fit any current definition – ie on NC with RA flow because we believe that this represents some CPAP. We will report by the physiologic as we have indicated but we will need to see how concordant the findings are between these 2 definitions. I certainly do not intend to use any of the preliminary analyses and am OK to wait.
The issue will be whether we find a difference between the groups or not – if no differences are found using either – no problem, if the same differences between the groups using either – no problem – If the results differ by diagnosis of BPD – Big problem
Some of the BPD data in the form is difficult. I will look and send you my thoughts on the questionable ones – I agree with the Y and Ns
In the Table about the eye outcomes – are infants represented only once? That is can an infant have a Zone 2 at last exam and also be < 55 weeks??
I look forward to seeing a final data set. I will work on Tables and get them back to you.

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, July 06, 2009 3:06 PM
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: BPD and ROP outcomes for SUPPORT

Attached is the list of infants missing the ROP final outcome with the result of the last exam the infant had, the estimated PMA at the time of the last exam, the current estimated PMA and whether the FU window for the infant has yet to open, is open now, or is closed.

Neil, I know that you are eager to look at the BPD results, but I had a couple of questions/comments on your request. One is that the physiologic definition of BPD (or death) is the primary outcome listed in the protocol (see below), so I'm not sure why we would look at traditional BPD (oxygen at 36 weeks) first. Also, although we are only missing data on 5 infants, in the past several days I have come up with a list of queries for the centers (about 40 so far) where there are inconsistencies in BPD-related data that need to be cleared up, particularly between forms (NG07, PHY01, SUPP11, etc.). I am actually still working on these checks, as they are rather tedious, but I hope to be finished with them tomorrow so that the queries can go out to the centers. Because the queries will impact the data, Abhik suggests that we hold off on running the BPD outcome until they are resolved. In the meantime, if you want to put together shells for tables that you would like to have in the paper I can put together the programming to produce them.

One other thing that would be helpful is if you would take a look at the attached spreadsheet which has the current classification of physiologic BPD for infants who were eligible for the challenge but have comments explaining why the challenge did not take place. If you have any revisions to make to those classifications, please let me know. There are also a couple of infants with a '?' for BPD where I would appreciate your input.

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Thanks,
Marie

From page 21 of the SUPPORT protocol:

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, July 05, 2009 5:51 PM
To: Gantz, Marie
Subject: RE: BPD and ROP outcomes for SUPPORT

Hi Marie
Please send me anything that we have for the BPD - a few missing infants will not change the final stats and I need to know what we found as soon as possible
I would start with BPD by oxygen at 36 weeks and we can later look at the Physiologic definition of BPD if the results differ
So for now if there are only 5 missing BPD infants let's do some of the study tables for demographics and the primary of survival without BPD, and the safety issues – death, air leaks DR compressions and Severe IVH
Lets also look at the number of ROP missing final diagnosis – I want to get a handle on how many are truly a problem of ascertainment.
Thanks for your help. I will not be sharing anything with anyone at this point until you feel we have a final data set for BPD and eventually for ROP which I know will be a bit more complex.
Thanks again
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, July 02, 2009 2:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Das, Abhik
Subject: BPD and ROP outcomes for SUPPORT

Hi all,

As is it is almost 5:00 and tomorrow is a holiday, I just wanted to let you know that I am still working on the listing of who is missing the BPD and ROP outcomes for SUPPORT based on this week's data. It has taken me a little longer this week because I have carefully reviewed all of the BPD data and come up with a comprehensive list of both missing data and cases where we have inconsistent data. Unless Rose

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objects, I will send her that list of queries in lieu of the usual missing data reminders for BPD this week. I will also send a breakdown of where we stand with respect to BPD and ROP, and the usual missing data reminders for ROP and NDI. You can expect those either later today or on Monday. FYI, we still have 5 infants for whom we are waiting on data for BPD (NG03 and NG07).

Have a great weekend!

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From: Gantz, Marie
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: BPD and ROP outcomes for SUPPORT
Date: Monday, July 06, 2009 6:05:38 PM
Attachments: SUPPORT infants with missing ROP 07-06-09.rtf
Other reasons challenge not done (send) 6-26-09.xls

Attached is the list of infants missing the ROP final outcome with the result of the last exam the infant had, the estimated PMA at the time of the last exam, the current estimated PMA and whether the FU window for the infant has yet to open, is open now, or is closed.

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Thanks again

Neil

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Sent: Thursday, July 02, 2009 2:00 PM
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Cc: Das, Abhik
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Have a great weekend!

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Reasons ROP is missing

The FREQ Procedure

Reason for no ROP classification				
noropreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1=Infant withdrawn	4	2.92	4	2.92
1=Estimated PMA<55 weeks	20	14.60	24	17.52
2=Lowest zone of any vessels is I at last exam	2	1.46	26	18.98
3=Lowest zone of any vessels is II at last exam	56	40.88	82	59.85
4=Lowest zone of any vessels is III for one exam	54	39.42	136	99.27
5=PMA>=55 weeks but no ROP exams entered	1	0.73	137	100.00

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=2=Lowest zone of any vessels is I at last exam

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels, previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels, previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
1	33	3	P	1	P	188	Y	N	3=Closed
2	47	1	2	1	2	234	Y	N	3=Closed

Reason for no ROP classification=3=Lowest zone of any vessels is II at last exam

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels, previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels, previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
3	35	2	2	2	2	56			1=Not open yet
4	39	2	2	2	2	57			.
5	35	2	2	2	2	61			1=Not open yet
6	37	2	2	2	2	62	Y		1=Not open yet
7	33	2	.	2	.	64			1=Not open yet
8	39	2	2	2	2	65	Y		1=Not open yet
9	42	3	2	2	2	70			1=Not open yet
10	41	2	2	2	2	70	Y		1=Not open yet
11	33	2	2	2	2	72			1=Not open yet
12	35	2	2	2	2	74			1=Not open yet
13	39	2	2	2	2	74	Y		1=Not open yet
14	37	2	2	2	2	78			1=Not open yet
15	35	2	2	2	2	79			1=Not open yet
16	34	2	2	2	2	81			1=Not open yet
17	38	2	2	2	2	83			1=Not open yet
18	36	2	2	2	2	90			1=Not open yet
19	38	2	1	2	1	95	Y		1=Not open yet
20	49	2	3	2	3	99	Y		1=Not open yet
21	43	2	2	2	2	101			1=Not open yet
22	42	2	2	2	2	101		N	1=Not open yet
23	50	2	2	2	2	102	Y		1=Not open yet
24	44	2	2	2	2	102	Y		1=Not open yet
25	38	2	2	2	2	104	Y		1=Not open yet
26	33	2	2	2	2	104	Y		1=Not open yet
27	36	2	2	2	2	106			1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at >55 weeks PMA	Final ROP status obtained at FU	FU window
28	41	2	2	2	2	110	Y		1=Not open yet
29	38	2	2	2	2	112			1=Not open yet
30	36	2	2	2	2	113			1=Not open yet
31	32	2	1	2	1	115			1=Not open yet
32	38	2	2	2	2	117	Y		1=Not open yet
33	36	2	2	2	2	119			2=Open now
34	65	2	2	2	2	119	Y	?	2=Open now
35	40	2	3	2	3	119	Y		2=Open now
36	39	3	2	2	2	119			2=Open now
37	41	2	2	2	2	124			2=Open now
38	77	2	2	2	2	127		N	2=Open now
39	34	2	2	2	2	128	Y	N	2=Open now
40	105	2	2	2	2	131		N	2=Open now
41	46	2	2	2	2	131		N	2=Open now
42	33	2	.	2	.	135	Y	N	2=Open now
43	33	2	.	2	.	135	Y	N	2=Open now
44	33	2	.	2	.	136	Y	N	2=Open now
45	44	2	2	2	2	137	Y		3=Closed
46	71	2	2	2	2	141		N	3=Closed
47	85	2	2	2	2	145	Y	N	3=Closed
48	39	2	2	2	2	147			3=Closed
49	55	9	2	9	2	148	Y	N	3=Closed
50	44	2	2	2	2	183	Y	N	3=Closed
51	43	2	2	2	2	195			3=Closed
52	37	2	2	2	2	197	Y		3=Closed
53	94	2	2	2	2	219	Y	N	3=Closed
54	34	2	2	2	2	219	Y	N	3=Closed
55	78	2	2	2	2	233	Y	N	3=Closed
56	35	2	2	2	2	240	Y	N	3=Closed
57	64	2	2	2	2	242	Y	N	3=Closed
58	36	2	2	2	2	242		N	3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=4=Lowest zone of any vessels is III for one exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
59	50	3	2	3	2	57			1=Not open yet
60	38	3	2	3	2	60			1=Not open yet
61	34	3	2	3	2	61	Y		1=Not open yet
62	36	3	.	3	.	62			1=Not open yet
63	38	3	2	3	2	63	Y		1=Not open yet
64	39	3	2	3	2	67	Y		1=Not open yet
65	40	3	2	3	2	71	Y		1=Not open yet
66	36	3	2	3	2	71	Y		1=Not open yet
67	37	3	2	3	2	74	Y		1=Not open yet
68	35	3	2	3	2	75			1=Not open yet
69	36	3	2	3	2	78	Y		1=Not open yet
70	46	3	2	3	2	81			1=Not open yet
71	41	3	2	3	2	82	Y		1=Not open yet
72	35	3	2	3	2	83	Y		1=Not open yet
73	41	3	2	3	2	86	Y		1=Not open yet
74	40	3	2	3	2	86	Y		1=Not open yet
75	36	3	2	3	2	90	Y		1=Not open yet
76	37	3	2	3	2	91	Y		1=Not open yet
77	39	3	2	3	2	92	Y		1=Not open yet
78	38	3	2	3	2	93			1=Not open yet
79	38	3	2	3	2	94			1=Not open yet
80	35	3	2	3	2	94	Y		1=Not open yet
81	39	3	2	3	2	98	Y		1=Not open yet
82	40	3	2	3	2	102	Y		1=Not open yet
83	33	3	2	3	2	103			1=Not open yet
84	34	3	2	3	2	104	Y		1=Not open yet
85	36	3	2	3	2	105			1=Not open yet
86	39	3	2	3	2	105			1=Not open yet
87	34	3	2	3	2	107	Y	?	1=Not open yet
88	41	3	2	3	2	107	Y		1=Not open yet
89	37	3	2	3	2	110	Y		1=Not open yet
90	36	3	2	3	2	119			2=Open now
91	44	3	2	3	2	128	Y		2=Open now
92	44	3	2	3	2	133			2=Open now

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels - previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
93	35	3	2	3	2	137	Y	N	3=Closed
94	39	3	2	3	2	147			3=Closed
95	37	3	2	3	2	148	Y	N	3=Closed
96	46	3	2	3	2	159	Y	N	3=Closed
97	36	3	2	4	2	161	Y		3=Closed
98	38	3	2	3	2	171	Y	N	3=Closed
99	44	3	2	3	2	215	Y		3=Closed
100	37	3	2	3	2	220	Y	N	3=Closed
101	55	3	2	3	2	222	Y		3=Closed
102	34	3	2	3	3	223		N	3=Closed
103	32	3	.	3	.	226	Y	N	3=Closed
104	33	3	P	3	P	227	Y	N	3=Closed
105	39	3	2	3	2	235	Y	N	3=Closed
106	36	3	2	3	2	236	Y	Y	3=Closed
107	33	3	P	3	P	238	Y	N	3=Closed
108	34	3	2	3	2	239	Y	N	3=Closed
109	86	3	2	3	2	239	Y	N	3=Closed
110	39	3	2	3	2	241	Y	N	3=Closed
111	88	3	2	3	2	246	Y	N	3=Closed
112	37	3	2	3	2	249	Y	N	3=Closed

Reason for no ROP classification=5=PMA>=55 weeks but no ROP exams entered

Obs	Estimated PMA on last ROP exam date	Left-lowest zone of any vessels	Left-lowest zone of any vessels - previous exam	Right-lowest zone of any vessels	Right-lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
113	.	.	.	.	.	58			1=Not open yet

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PHY01_reasons

Infant	Reason code	Other reason specified/comment	BPD	MG note
1	2=Increased support	pt was intubated for surgery and we have been unable to wean off.	?	RA by NC per PHY01. Per SUPP11, no support at 6:00, on vent at 24:00. (Will clarify RA by NC vs. no support with center.)
2	3=Instability	Bloody stool	Y	On supp O2 by NC per NG07.
3	6=Weaned to RA	weaned to room air 4/22/08	N	36 wks on 4/21.
4	6=Weaned to RA	100% RA on 3/25/07	N	36 wks on 3/21.
5	6=Weaned to RA	to RA 9/24 6A eval for test 9/25/06	N	36 wks on 9/23.
6	6=Weaned to RA	physiologicf evaluation was scheduled for 8/14 and infant was in room air	N	36 wks on 8/13.
7	6=Weaned to RA	Infant was scheduled for physiologic evaluation on 10/30/2007 but was in room air	N	36 wks on 10/28.
8	6=Weaned to RA	Patient weaned to RA on 11/13/07	N	36 wks on 11/12.
9	6=Weaned to RA	Patient weaned to RA on 11/13/07	N	36 wks on 11/12.
10	6=Weaned to RA	RA 11/30/08	N	36 wks on 11/25.
11	9=Other (explain)	pt in ra on day of scheduled challenge. only receiving cannula feedings	N	
12	9=Other (explain)	patient was in RA for most of the day when challenger was scheduled	N	
13	9=Other (explain)	weaned to room air on day planned challenge	N	
14	9=Other (explain)	infant failed weaning attempts multiple times. Physician preferred to defer this challenge.	Y	On supp O2 by NC per NG07.
15	9=Other (explain)	discharged home on 02 before challenge could be done	Y	DC 4 days past 36 weeks. Supp O2 by NC at 36 wks and status per NG07.
16	9=Other (explain)	policy not in place yet	Y	On supp O2 by NC per NG07.
17	9=Other (explain)	Personnel not available	Y	RA by NC with flow 2 lpm per SUPP11.
18	9=Other (explain)	personnel not available	Y	RA by NC with flow 1 lpm per SUPP11.
19	9=Other (explain)	second site not certified to perform physiologic eval	Y	On supp O2 by NC per NG07.
20	9=Other (explain)	second site not certified to do physiologic eval	Y	On supp O2 by NC per NG07.
21	9=Other (explain)	After delivery infant was found to have trisomy 21. Doctor wanted the infant on NC for cardiac purposes.	N	
22	9=Other (explain)	The infant had just increased support to 2L vapotherm from a NC due to numerous desaturations. Still unclear if vapotherm was considered CPAP or NC	Y	Per Neil email 1/23/07.
23	9=Other (explain)	personnel not available to do reduction.	Y	On supp O2 by NC per NG07.
24	9=Other (explain)	patient discharged prior to performing reduction	Y	DC 1 day past 36 weeks. Supp O2 by NC at 36 wks and status per NG07.
25	9=Other (explain)	has desats with feedings, cannot wean osygen	Y	On supp O2 by NC per NG07.
26	9=Other (explain)	patient in room air at 36 weeks, but at discharge went home on oxygen	N	DC at 42 6/7 weeks PMA.
27	9=Other (explain)	RESEACH STAFF UNAVALILABLE	Y	On supp O2 by NC per NG07.
28	9=Other (explain)	Baby's effective FiO2 at altitude did not fit criteria.	Y	On supp O2 by NC per NG07.
29	9=Other (explain)	Baby's effective FiO2 at altitude did not fit criteria.	Y	On supp O2 by NC per NG07.
30	9=Other (explain)	Pt's effective Fi02 at altitude did not fit critera.	Y	On supp O2 by NC per NG07.

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31	9=Other (explain)	According to scale, infant does not have BPD. On NC 1/2L (0.5L) with Fi02 21-23%.	?	On RA by NC per NG07 and SUPP11.
32	9=Other (explain)	Pt's effective Fi02 at altitude did not fit criteria.	Y	On supp O2 by NC per NG07.
33	9=Other (explain)	NNP declined reduction testing because baby had been up to 3 lpm from 2 lpm because she was having and continued to have a lot of apnea desaturations (1-2 per	Y	Receiving support by NC with flow >.5 lpm.
34	9=Other (explain)	On day of evaluation infant's weight was 2085g and he was on 1/2 L flow of 23%. According to chart he did not have BPD.	Y	Receiving supplemental O2 (FiO2=.23) by NC.

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From: Wally Carlo, M.D.
To: Alexis Davis; Krisa Van Meurs
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ANS manuscript
Date: Wednesday, July 01, 2009 6:34:25 PM

Hi Alexis:

Yes, I will take this on as soon as I submit the cytokine paper which should happen in about two weeks. I would love to have you as a co-author as I know of your interest in this area.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: [redacted] [mailto[redacted] **On Behalf Of** Alexis Davis
Sent: Wednesday, July 01, 2009 3:22 PM
To: Wally Carlo, M.D.; Krisa Van Meurs
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ANS manuscript

Dr. Carlo-

Krisa mentioned that you and she spoke at the Network meeting about getting back to work on the antenatal steroids manuscript. I have attached comments (in green) in response to your thoughts (in red) from last August to serve as a platform for a conference call to discuss what the next steps might be to complete the project. I hope to be able to contribute ideas for analysis and perhaps help to finalize the manuscript to support my role as a contributing author for the project.

I am finishing up travel for the Preemie aEEG pilot in the next two weeks but could be available beginning the week of July 20th. Let me know what your schedule looks like or if you have an administrative person that I should work with to get this set up.

Thanks and have a good holiday weekend-
Alexis

--
Alexis Davis, MD
Instructor, Neonatology
Stanford University
office: (650) 723-5711
pager (650)[redacted]
email: alexis.davis@stanford.edu

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From: Cassandra Hudson

To: Abbot Laptook; Abhik Das; Av Fanaroff; Barbara Stoll; Bill Oh; Brad Yoder; Brenda Poindexter; Carolyn Petrie Huitema; David P. Carlton; David Stevenson; Dennis Wallace; Ed Donovan; Edward Bell; Ivan Frantz; Jon Tyson; Kathleen Kennedy; Ken Poole; Krisa P. Van Meurs; Kristi Watterberg; Kristin Zaterka-Baxter; Kurt Schibler; Meg Cunningham; Michele C. Walsh; Mickey Caplan; Mike Cotten; Namasivayam Ambalavanan; Pablo Sanchez; Richard Ehrenkranz; Robin Ohls; Roger Faix; Ron Goldberg; Higgins, Rosemary (NIH/NICHD) [E]; Seetha Shankaran; Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]

Subject: Manuscript for Review 7/1/2009 - Antenatal Consent Paper

Date: Wednesday, July 01, 2009 3:08:13 PM

Attachments: Antenatal_Consent_Paper_6_24.doc

Dear PIs,

The attached manuscript has been submitted to the Publication Subcommittee for internal review. The manuscripts are being sent to you as a courtesy. If you wish, you may share comments with the first author. Please do not share the manuscripts with others or duplicate.

Thanks,
Wally

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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Keywords: Informed Consent, Antenatal, Neonatal

The authors have no financial disclosures or conflicts of interest.

ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT (24 0/7 to 27 6/7 wk GA) were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled i.e., consent was given but study-prescribed interventions was not undertaken . Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD

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Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

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This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically

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to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All

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data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision. (Did an MD making the first approach for consent have any influence on the success rate?)

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Infants of non-approached and approached mothers were different in several important ways (Table 2). Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). (The N is large enough that p values of this magnitude for relatively small differences are not that surprising. Other than the clearly large and important difference in antenatal steroids, are any of these other differences thought to be clinically significant as well as statistically significant?) A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, $p<.0001$). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance ($p=0.0011$) and to have received prenatal care ($p=0.0039$), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, $p<0.0001$) (Table 3).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who

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did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or

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consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[12] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid

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recipients in the non-participant group in a minimal risk emergency department study.[13] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[14]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates,

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and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

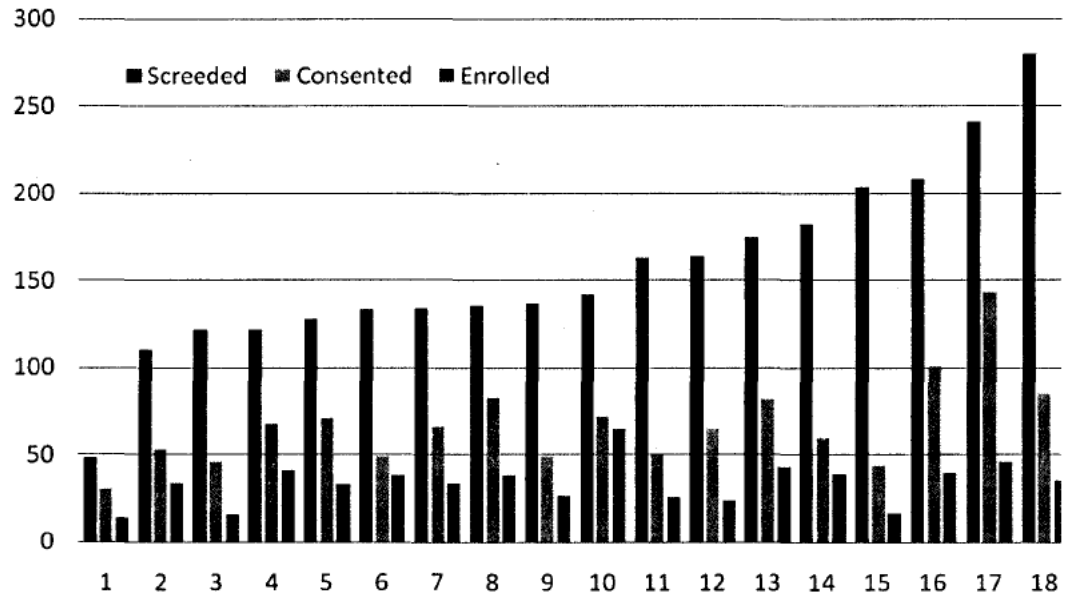

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2

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Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 1. Reasons for not approaching mothers for consent.

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039
No Antenatal Steroids	3.8	15.7	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Screened (n = 2828 Women)

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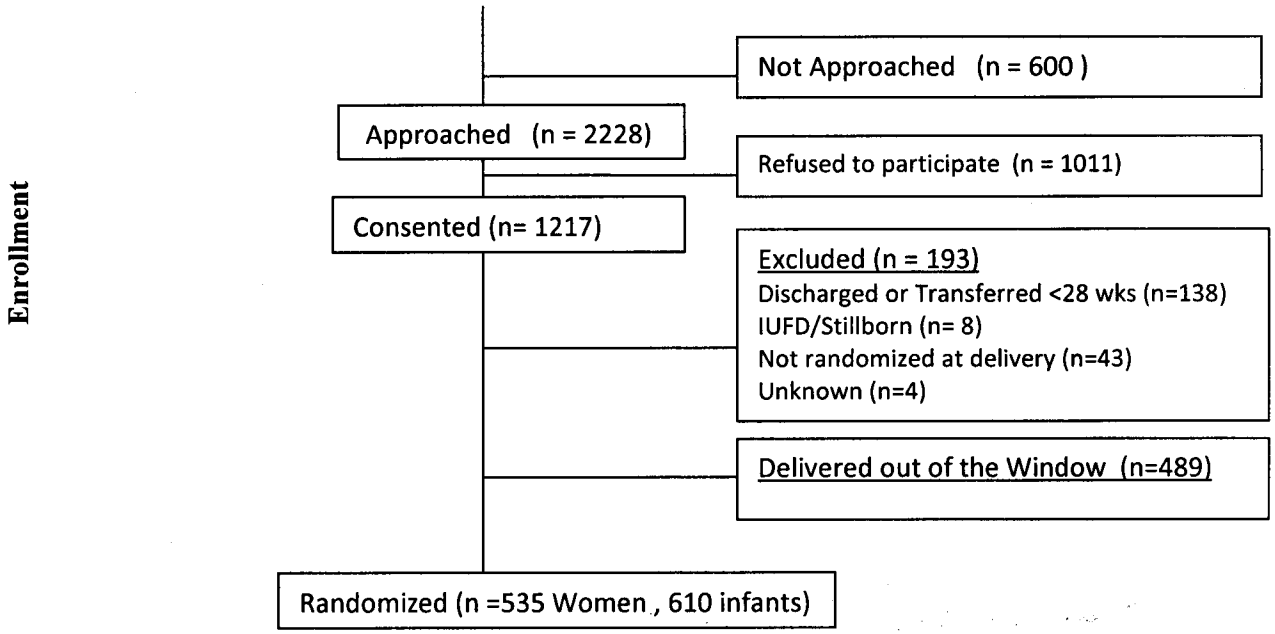

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Cassandra Hudson
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Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Manuscript for Review 7/1/2009 - Antenatal Consent Paper
Date: Wednesday, July 01, 2009 2:27:18 PM
Attachments: Antenatal Consent Paper 6 24.doc

Dear Krisa,
Attached is a manuscript entitled "Antenatal Consent in a Large Multicenter Trial – At What Cost?" Would you be able to review the manuscript for the NICHD Neonatal Research Network by July 15 (two weeks)? There are no particular guidelines for the review except to look at study design, validity, clarity of results, and appropriateness of interpretation.

Please send the review to me. We will keep your name confidential.

Please let me know within 72 hours if you will be unable to do the review
Thanks,
Wally

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT (24 0/7 to 27 6/7 wk GA) were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled i.e., consent was given but study-prescribed interventions was not undertaken . Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD

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Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

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This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically

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to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All

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data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the inability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision. (Did an MD making the first approach for consent have any influence on the success rate?)

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Infants of non-approached and approached mothers were different in several important ways (Table 2). Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). (The N is large enough that p values of this magnitude for relatively small differences are not that surprising. Other than the clearly large and important difference in antenatal steroids, are any of these other differences thought to be clinically significant as well as statistically significant?) A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, $p<.0001$). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance ($p=0.0011$) and to have received prenatal care ($p=0.0039$), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, $p<0.0001$) (Table 3).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who

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did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers also belonged to a maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or

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consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[12] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid

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recipients in the non-participant group in a minimal risk emergency department study.[13] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[14]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates,

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and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

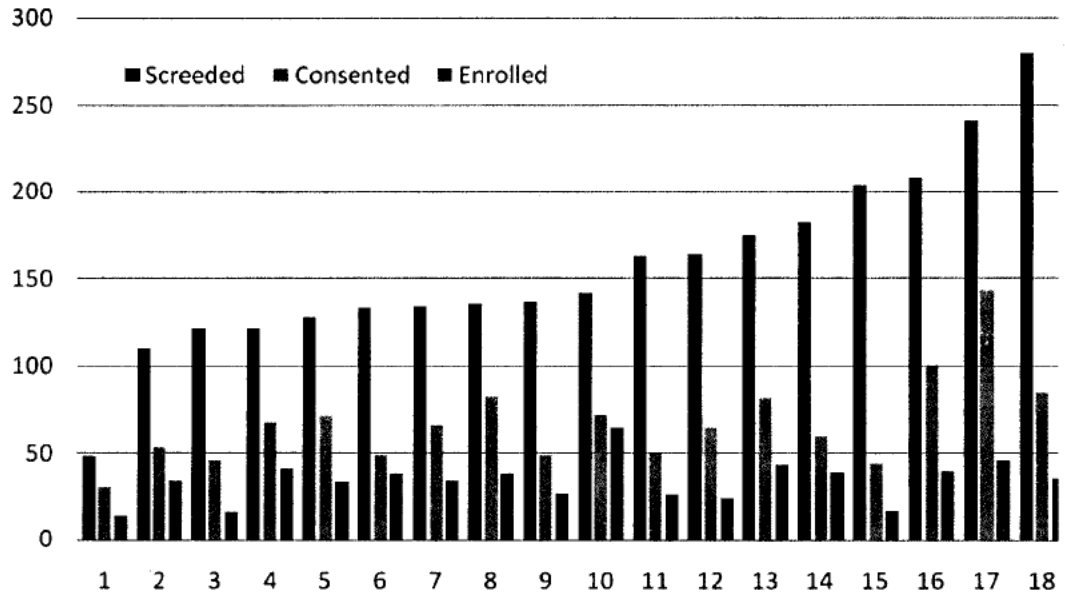

Figure 1. Women who were screened, consented, and enrolled by Center

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2

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Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 1. Reasons for not approaching mothers for consent.

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 2. Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039
No Antenatal Steroids	3.8	15.7	<.0001

Table 3. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Screened (n = 2828 Women)

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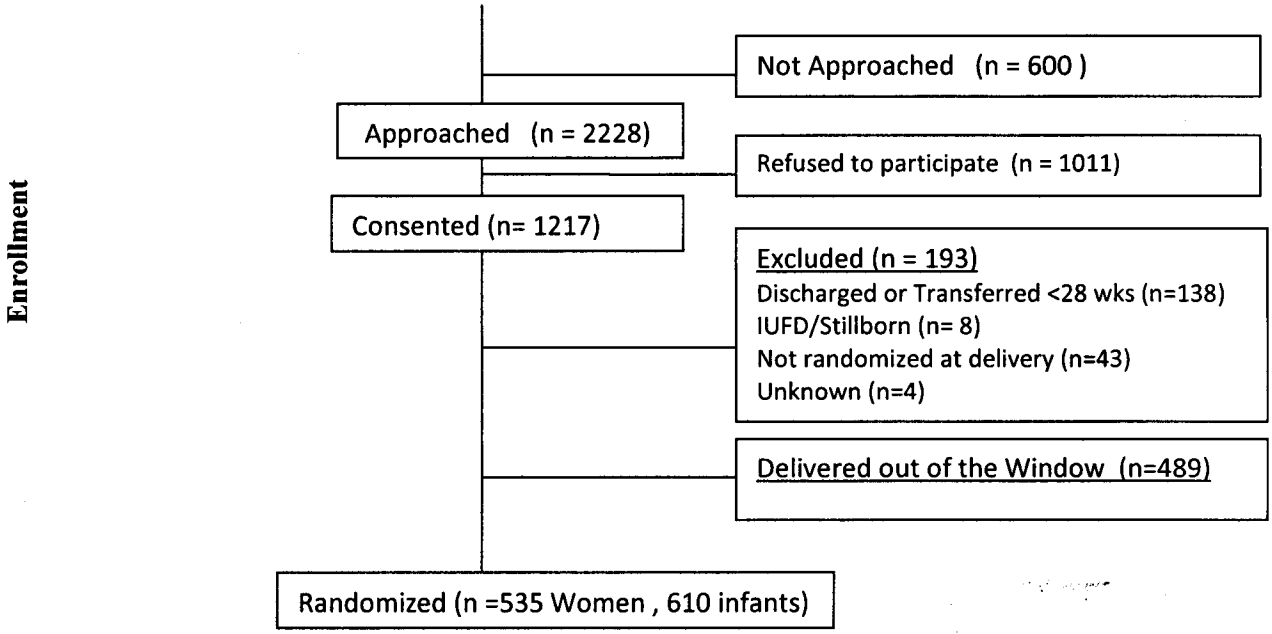

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Finer, Neil
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Cc: Rich, Wade; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT Updates
Date: Friday, June 26, 2009 9:14:27 AM
Attachments: Antenatal Consent Paper 6_15 .doc

Hi Rose
I will present this email only for the steering committee. Can it be projected?

SUPPORT Update 6/19/2009

Total enrollment of 1317 was completed in February 2009. The primary outcomes of BPD/death and ROP/death are still unknown for 14 and 140 infants, respectively.

	ROP/death		
BPD/death	**Known**	**Unknown**	**Total**
Known	1172	131	1303
Unknown	5	9	14
Total	1177	140	1317

Infants with known outcomes for BPD/death and ROP/death

The last SUPPORT infant reached 36 weeks PMA in late May, so we should have complete data on the BPD outcome shortly. Historically, by 55 weeks PMA we have known ROP status for 100% of the infants with an adverse outcome and about 92% of the infants with a positive outcome. The last SUPPORT infant will reach 55 weeks PMA at the end of September.

To date, 778 (59%) of SUPPORT infants have a known outcome for NDI/death at 18-22 months adjusted age. The last follow up window will open in December 2010 and will close in April 2011.

Plans:

I will be starting to develop the manuscript
We are planning a visit to RTI and Wally will join us there at the end of August – hopefully when we can close the neonatal endpoints of ROP/BPD. We should have the BPD data within a few weeks
The plan is to develop 2 manuscripts –
CPAP vs Surfactant
High vs Lower SpO2

I suspect that we will be ready with the first within 2 months
And the second in 3 months
We would obviously submit as soon as they are ready – Probably NEJM

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We need to complete the follow-up and we are well on the way with almost 60% of those outcomes available
The very first manuscript will be the consent manuscript which is now circulating to the authors. I have attached for your comments

Points for discussion:

1. Where should the data be presented??

It will be ready well ahead of PAS.
There will probably be new data for PAS – Secondaries etc

2. Need status reports for all secondaries
3. Continue to get all final infant data, especially ROP data, and complete follow-up

Safe travels
Neil

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled. Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the

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study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to

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the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

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2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the ability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways as shown in Table 1. Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to

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antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance (p=0.0011) and to have received prenatal care (p=0.0039), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, p<0.0001) (Table 2).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers belonged to a second maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

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Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for

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all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[12] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[13] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[14]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point

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toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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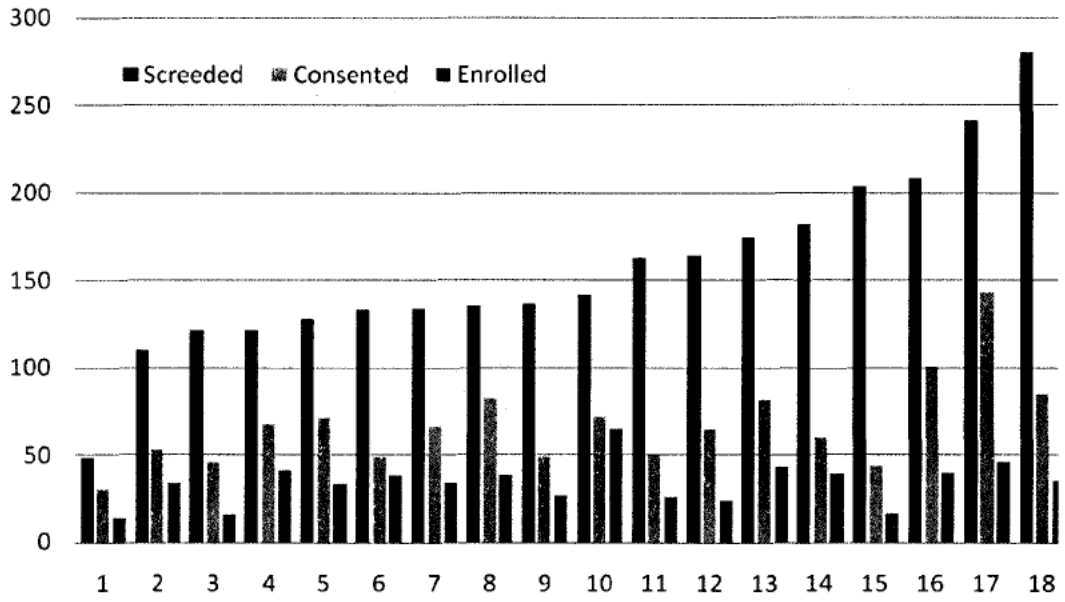

Figure 1. Women who were screened, consented, and enrolled by Center

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 1 Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039

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No Antenatal Steroids	3.8	15.7	<.0001

Table 2. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 2 Reasons for not approaching mothers for consent.

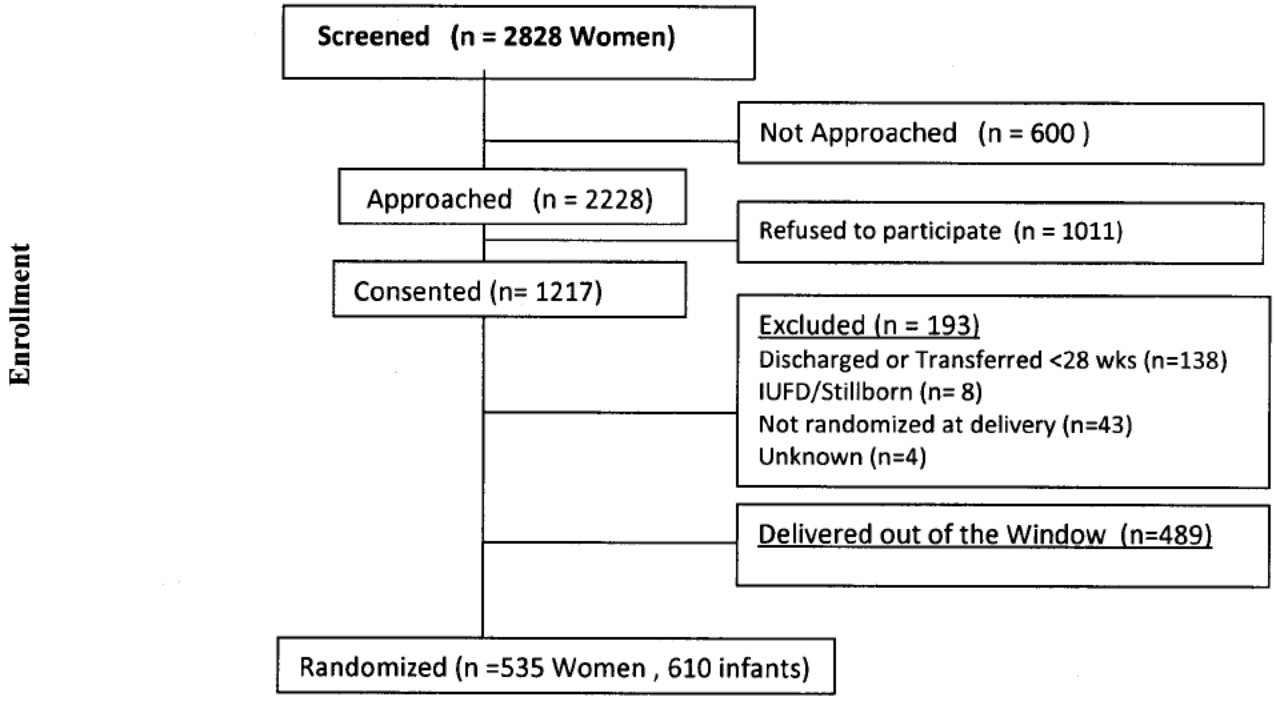

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Finer, Neil
To: "Roger Faix"; Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; "Michele Walsh"; Bradley Yoder; "Abbot Laptook"; "kurt.schibler@cchmc.org"; "Das, Abhik"; "Nancy Newman"; "Gantz, Marie"; "Poole, W. Kenneth"
Cc: "Petrie, Carolyn"; "Zaterka-Baxter, Kristin"; Rich, Wade; Martinez, Fernando
Subject: RE: SUPPORT Updates
Date: Wednesday, June 24, 2009 2:29:01 PM

Many thanks Roger
Neil

From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Wednesday, June 24, 2009 10:53 AM
To: Finer, Neil; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; Bradley Yoder; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade; Martinez, Fernando
Subject: RE: SUPPORT Updates

Hi all!

I had the opportunity to look over Wade's antenatal consent manuscript and have made comments on the attached version of that manuscript. Items in pink font are questions/suggestions; items in plum font are additions; while those items in red font are for deletion. I hope these thoughts are useful!

Roger

From: Finer, Neil [nfiner@ucsd.edu]
Sent: Sunday, June 21, 2009 11:35 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; Bradley Yoder; Roger Faix; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade; Martinez, Fernando
Subject: RE: SUPPORT Updates

Hello Everyone
Congratulations on a job very well done!!
Marie has prepared the following summary for our meeting

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2. Need status reports for all secondaries
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4. Any additional bisuness??

Safe travels
Neil

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From: Laptook, Abbot
To: Webb, Robin E.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT call
Date: Wednesday, June 24, 2009 2:13:06 PM

Robin
Are these dates realistic; I realize neil is incredibly enthusiastic but we just had a call yesterday and data needs to be collated, made sure there are no glaring issues etc before it is worthwhile to get everyone on a call to discuss. AL

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Wednesday, June 24, 2009 1:11 PM
To: Laptook, Abbot; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: Webb, Robin E.; Newman, Jamie; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Vecchio, Brenda; Cunningham, Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin
Subject: SUPPORT call

We need to schedule a SUPPORT call to discuss data analysis and progress. Please send your availability for the days below, indicating time zone if other than ET.

Robin Webb
RTI, International
6110 Executive Blvd, Suite 902
Rockville, MD 20852

Wed 7/1

Mon 7/6
Tues 7/7
Wed 7/8

Mon 7/13
Tues 7/14
Wed 7/15
Thurs 7/16
Fri 7/17`

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From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: another SUPPORT call
Date: Tuesday, June 23, 2009 4:40:42 PM

I was just looking at the email his assistant sent. He's on (b) (6) [redacted]. Do you want to skip those weeks and go into mid-August?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 23, 2009 4:25 PM
To: Webb, Robin E.
Subject: RE: another SUPPORT call

Yes, we want him
Go a week or two later
Rose

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Tuesday, June 23, 2009 4:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: another SUPPORT call

Hi Rose,

Is Carlo essential for this call? I was going to poll for the first 3 full weeks in June for this but I see Carlo is only available like 3 days out of those 3 weeks, so it may be difficult to come up with a time in mid-July if he has to be on the call.

Thanks,
Robin

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 23, 2009 2:06 PM
To: Webb, Robin E.
Subject: another SUPPORT call

Robin
Can you set up another call with the SUPPORT Subcommittee in mid-July to discuss data analysis and progress?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575

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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Wally Carlo, M.D.
To: Zaterka-Baxter, Kristin; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Huitema, Carolyn Petrie; Rich, Wade; Martinez, Fernando
Subject: RE: REMINDERL SUPPORT Subcommittee call today at 1:00PM EST
Date: Tuesday, June 23, 2009 12:20:09 PM

A confict has come up and I will not be able to be on the call today. Sorry.

Wally

-----Original Message-----
From: "Zaterka-Baxter, Kristin" <kzaterka@rti.org>
To: "Finer, Neil" <nfiner@ucsd.edu>; "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Michele Walsh" <mcw3@case.edu>; "Bradley Yoder" <Bradley.Yoder@hsc.utah.edu>; "Roger Faix" <Roger.Faix@hsc.utah.edu>; "Abbot Laptook" <ALaptook@wihri.org>; "kurt.schibler@cchmc.org" <kurt.schibler@cchmc.org>; "Das, Abhik" <adas@rti.org>; "Nancy Newman" <nxs5@case.edu>; "Gantz, Marie" <mgantz@rti.org>; "Poole, W. Kenneth" <poo@rti.org>
Cc: "Huitema, Carolyn Petrie" <petrie@rti.org>; "Rich, Wade" <wrich@ucsd.edu>; "Martinez, Fernando" <fmartinez@ucsd.edu>
Sent: 6/23/2009 7:16 AM
Subject: REMINDERL SUPPORT Subcommittee call today at 1:00PM EST

Hi all;

Reminder for today's call at 1:00 PM EST:

Dial:

Within the USA

866-675(b) (6)

or

Outside the USA

1-203-310-(b) (6)

Then, enter Participant Passcode:

(b) (6)

Thanks,

Kris

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, June 21, 2009 1:35 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; Das, Abhik; 'Nancy Newman'; Gantz, Marie; Poole, W. Kenneth
Cc: Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Rich, Wade; Martinez, Fernando
Subject: RE: SUPPORT Updates

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BPD/death

ROP/death

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Known

1172

131

1303

Unknown

5

9

14

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Cc: Huitema, Carolyn Petrie; Rich, Wade; Martinez, Fernando
Subject: REMINDERL SUPPORT Subcommittee call today at 1:00PM EST
Date: Tuesday, June 23, 2009 8:16:10 AM

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From: Susan Hintz
To: Vaucher, Yvonne
Cc: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; mcunningham@rti.org
Subject: Re: Support Conference Call 06/22/09
Date: Monday, June 22, 2009 3:43:41 PM
Attachments: SDQP4-10_NOimpact.pdf
SDQ_P4-10_Impact.pdf
ChandlerSCQValidation2007.pdf
CharmanEfficacy3AutismScreeners2007.pdf
nimhautismspectrum.pdf

Thanks Yvonne!

We will make sure you are on the SUPPORT Extended follow-up list. It is great having you on the conference calls.

Attached are the papers and the NIMH statement.

I am also attaching the 2 versions of the SDQ if you didn't get those. I think Gerry was referring to the fact that the "impact questions" at the end of the one version of the SDQ could not replace the Impact on the Family Questionnaire, but also that there really might not be much added by doing the Impact on the Family, particularly given that we do not have a specific question related to this instrument vis a vis the MRI secondary findings or the main trial.

Your points about timing of training and about Saturday visits are interesting and insightful. It would be interesting to see the days of the week that Hypothermia visits were done routinely. I know that half our visits were home visits!

Susan

> Susan,
>
> Good conference call, focused and moved right along.
>
> Could we extract the financial questions from the "Impact on the Family" questionnaire which would save time but give us potentially useful information? Did Gerry infer that if we had "extra" time there are additional psychometry items that he would like add?
>
> For the 1st Support cohort, we could do the training early (?August/September) for Stanford and UCSD out here; then do the training for everyone the next year (maybe also a bit earlier than usual given when the windows open.) We did this for Hypothermia as UCSD joined the Network at the end of the study so didn't participate in the training until the second year when our children's windows opened.

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We have had to do several Saturday visits for Hypothermia due to space and personnel availability as well as reluctance of the family to take a day off from work, especially if they have to travel. It may take two days altogether to get here so the child is fresh in the AM. Maybe more of a problem for us as we have a small program with limited staff and space.

PS. Please add me to your Support FUP e-mail list so I can keep up to date. If you have a chance, and it is convenient, could you please forward the paper that Betty sent, the Chandler paper and the NIMH autism statement that were distributed?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.

Attending Neonatologist

Director, Infant Special Care Follow-Up Program

Division of Neonatal/Perinatal Medicine

Professor of Pediatrics

UCSD School of Medicine

tele: 619-543-3759

FAX: 619-543-3812

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Susan R. Hintz, M.D., M.S. Epi

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Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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Strengths and Difficulties Questionnaire

P or T 4-10

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain. Please give your answers on the basis of the child's behavior over the last six months or this school year.

Child's name ..... Male/Female

Date of birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children, for example toys, treats, pencils	☐	☐	☐
Often loses temper	☐	☐	☐
Rather solitary, prefers to play alone	☐	☐	☐
Generally well behaved, usually does what adults request	☐	☐	☐
Many worries or often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, depressed or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often offers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets along better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Good attention span, sees work through to the end	☐	☐	☐

Signature ..... Date .....

Parent / Teacher / Other (Please specify):

Thank you very much for your help

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Steals from home, school or elsewhere	☐	☐	☐
Gets along better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Good attention span, sees chores or homework through to the end	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

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Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behavior or being able to get on with other people?

No	Yes-minor difficulties	Yes-definite difficulties	Yes-severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

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Validation of the Social Communication Questionnaire in a Population Cohort of Children With Autism Spectrum Disorders

SUSIE CHANDLER, PH.D., TONY CHARMAN, PH.D., GILLIAN BAIRD, F.R.C.P.C.H., EMILY SIMONOFF, F.R.C.PSYCH., TOM LOUCAS, PH.D., DAVID MELDRUM, F.R.A.C.P., MIMI SCOTT, R.G.N., AND ANDREW PICKLES, PH.D.

ABSTRACT

Objective: To examine the properties of the Social Communication Questionnaire (SCQ) in a population cohort of children with autism spectrum disorders (ASDs) and in the general population. **Method:** SCQ data were collected from three samples: the Special Needs and Autism Project (SNAP) cohort of 9- to 10-year-old children with special educational needs with and without ASD and two similar but separate age groups of children from the general population ($n = 411$ and $n = 247$). Diagnostic assessments were completed on a stratified subsample ($n = 255$) of the special educational needs group. A sample-weighting procedure enabled us to estimate characteristics of the SCQ in the total ASD population. Diagnostic status of cases in the general population samples were extracted from child health records. **Results:** The SCQ showed strong discrimination between ASD and non-ASD cases (sensitivity 0.88, specificity 0.72) and between autism and nonautism cases (sensitivity 0.90, specificity 0.86). Findings were not affected by child IQ or parental education. In the general population samples between 4% and 5% of children scored above the ASD cutoff including 1.5% who scored above the autism cutoff. Although many of these high-scoring children had an ASD diagnosis, almost all (~90%) of them had a diagnosed neurodevelopmental disorder. **Conclusions:** This study confirms the utility of the SCQ as a first-level screen for ASD in at-risk samples of school-age children. *J. Am. Acad. Child Adolesc. Psychiatry* 2007;46(10):1324–1332. **Key Words:** autism, autism spectrum disorders, pervasive developmental disorders, screening, identification, SNAP cohort.

Accepted May 22, 2007.

Profs. Chandler and Baird are with Guy's and Thomas' NHS Foundation Trust, London; Prof. Charman is with UCL Institute of Child Health, London; Prof. Simonoff is with the Institute of Psychiatry, Kings College London; Dr. Loucas is with School of Psychology and Clinical Language Sciences, University of Reading, UK; Dr. Meldrum is with Chatswood Assessment Centre, Sydney; Ms. Scott is with East Sussex Hospitals NHS Trust, UK; and Prof. Pickles is with Division of Epidemiology & Health Sciences, University of Manchester, UK.

The study was funded by the Wellcome Trust and the Department of Health, United Kingdom. The authors are grateful to the children and families who participated in the study and to the clinical teams, whose collaboration made the study possible. They thank the expert group, Patrick Bolton, Antony Cox, Anne Gilchrist, Rebecca Landa, Ann Le Couteur, Catherine Lord, Lennart Pedersen, and Michael Rutter. Thanks also to Iris Carcani-Rathwell, Greg Pasco, Samantha Ross, Emma Rowley, Vicky Slonims, and Martha Turner for their help with assessments.

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The prevalence of autism spectrum disorders (ASDs), the common clinical term for the pervasive developmental disorders (PDDs) described in the psychiatric classification systems, *DSM-IV-TR* (American Psychiatric Association, 2000) and *ICD-10* (World Health Organization, 1993), is now recognized to be between 60 and 116/10,000, depending on the strictness with which the diagnostic criteria are applied (Baird et al., 2000, 2006; Chakrabarti and Fombonne, 2001, 2005; Green et al., 2005; Honda et al., 2005). Diagnosis requires careful history-taking and observation. However, screening questionnaires can help highlight a group requiring more in-depth diagnostic assessment. The Social Communication Questionnaire (SCQ; Rutter et al., 2003) is a recently developed screening tool for ASD based on the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and is increasingly widely used in clinical research and practice. In the

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initial validation study the SCQ discriminated well between ASD and non-ASD cases with a sensitivity of 0.85 and a specificity of 0.75 (Berument et al., 1999). The ability of the SCQ to discriminate between ASD and non-ASD cases in two samples of 3- to 6-year-old children has recently been reported. Eaves et al. (2006a) found reduced sensitivity (0.71) in one study and reduced specificity (0.54) in a second study (Eaves et al., 2006b). Several other first-level screens for identifying potential cases of ASD have also been recently published, including the Social and Communication Disorders Checklist (Skuse et al., 2005) and the Social Responsiveness Scale (Constantino and Gruber, 2005).

The initial validation study of the SCQ (Berument et al., 1999) had a number of limitations on the generalizability of its findings; the study was carried out with subjects who had previously completed the ADI-R, thus introducing potential response bias; the subjects were recruited from a number of different research studies and clinical sources, and many participants with autism were adults, but the non-ASD participants were predominantly children.

The first aim of the present study was to examine the instrument properties of the SCQ in a population cohort of children with special educational needs (SENs) with and without ASD. The second aim was to explore how the SCQ performed in samples of similar-age children from the general population with whom the SCQ has not previously been used.

METHOD

The study was approved by the South East Multicentre Research Ethics Committee (REC) (00/01/50), East Sussex Local REC (04/Q/1905/6), and West Kent Local REC (153/8/02).

SCQ

Screening of all of the children was carried out using the SCQ (Rutter et al., 2003). The SCQ is a parent-report questionnaire asking about characteristic autistic behavior at the age of 4 to 5 years and currently. Total scores can range from 0 to 39. It is based on the ADI-R (Lord et al., 1994) and has established validity with the ADI-R and a diagnosis of autism (Berument et al., 1999).

Samples

SCQ data were collected from three different samples: Special Needs and Autism Project (SNAP) sample, a cohort of children at risk of ASD due either to having received a local clinical ASD diagnosis or having a Statement of Special Educational Needs (Baird et al., 2006; a Statement of Special Educational Needs is a legal document issued by the UK local educational authority when children require significant additional support in school due to any learning and/or behavioral problems); a group of children without a Statement of Special Educational Needs from mainstream schools (school sample); and a group of children living in one postal district in the same geographic area (general population sample).

At-Risk (SNAP) Cohort

As part of a prevalence study of ASD, of a total population cohort of 56,946 children born between July 1, 1990 and December 31, 1991 (Baird et al., 2006), all of those with a current clinical diagnosis of PDD (n = 255) or considered at risk of being an undetected case by virtue of having a Statement of Special Educational Needs (n = 1,515) were screened. A total of 1,066 completed SCQs were returned (mean return rate 60.2%), 31 families declined further participation, leaving 1,035 (return rate 58.5%) who returned the SCQ and opted in for further assessments (see Figure 1 for sample ascertainment). Mean (SD) age at screening in this SEN/ASD sample was 10.3 (0.4) years.

A stratified subsample (by coincidence also n = 255) received a comprehensive diagnostic assessment including standardized clinical observation (Autism Diagnostic Observation Schedule-Generic [ADOS-G]; Lord et al., 2000) and parent interview assessments of autistic symptoms (ADI-R; Lord et al., 1994), language and IQ, psychiatric comorbidities, and a medical examination. The age at which participants were assessed ranged from 9.8 to 14.5 years. The team used *ICD-10* research criteria to derive a clinical consensus diagnosis of childhood autism (n = 81) and other ASDs (n = 77; see Baird et al., 2006 for details). Of the 77 cases meeting criteria for other ASDs, three met *ICD-10* criteria for atypical autism due to late onset, three met *ICD-10* criteria for atypical autism due to an insufficient number of areas of abnormality, 61 met *ICD-10* criteria for atypical autism due to subthreshold symptomatology, 7 met *ICD-10* criteria for PDD unspecified due to lack of information (incomplete assessment, adopted children for whom early history was not available), and 3 met *ICD-10* criteria for overactive disorder associated with mental retardation and stereotyped movements. Ninety-seven children did not meet clinical consensus diagnosis for autism or other ASD. Ninety-six of the non-ASD children were assigned *ICD-10* diagnoses following assessment; these included intellectual disability (*DSM-IV-TR* mental retardation) and learning disabilities (n = 56), language delay (n = 12), hyperkinetic and/or conduct disorder (n = 14), and a variety of other medical, sensory, and developmental diagnoses (n = 15). One child had a Statement of Special Educational Needs but did not meet *ICD-10* criteria for any developmental disorder.

For 36 randomly selected cases, project consensus diagnoses were compared to those of eight internationally recognized experts using *ICD-10* criteria (usually two experts independently rated ADI-R, ADOS, psychometric findings, and a clinical vignette for each case. Quadratic weighted agreement between project consensus and expert autism/ASD/no ASD diagnostic categories was 93% with κ = .77 (see Baird et al., 2006 for details).

The following child characteristics relevant to identification by the screen were also collected: IQ, severity of autism symptoms measured by ADI-R and ADOS-G algorithm total scores and parent report of emotional and behavioral problems. A total count of *ICD-10* symptoms (0–12) was systematically completed as part of the diagnostic review process of every case. Adaptive behavior was assessed using the Vineland Adaptive Behavior Scales (VABS; Sparrow et al., 1984).

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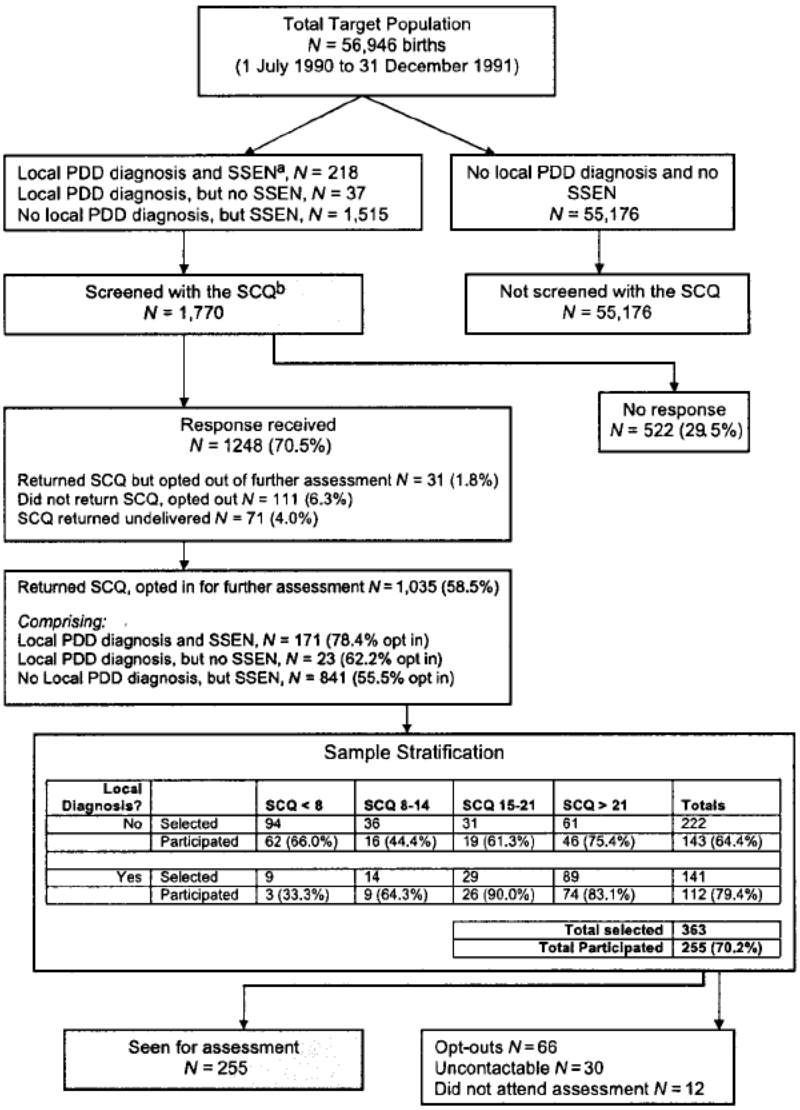

Local Diagnosis?		SCQ < 8	SCQ 8-14	SCQ 15-21	SCQ > 21	Totals
No	Selected	94	36	31	61	222
	Participated	62 (66.0%)	16 (44.4%)	19 (61.3%)	46 (75.4%)	143 (64.4%)
Yes	Selected	9	14	29	89	141
	Participated	3 (33.3%)	9 (64.3%)	26 (90.0%)	74 (83.1%)	112 (79.4%)

Total selected	363
Total Participated	255 (70.2%)

Fig. 1 Case ascertainment Special Needs and Autism Project (SNAP) sample. [a]SSEN = Statement of Special Educational Needs (see text). [b]SCQ = Social Communication Questionnaire. Reprinted from *The Lancet*, 368, Baird et al., Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP), 210–215. Copyright (2006), with permission from Elsevier.

IQ was measured using the WISC-III-UK (Wechsler, 1992), Raven's Standard Progressive Matrices or Colored Progressive Matrices (Raven et al., 1990a,b), depending on the child's ability. For the 35 cases in which Standard Progressive Matrices or Colored Progressive Matrices but not WISC Full Scale IQs (FSIQs) were available, imputed FSIQs were obtained using the regression relationship of FSIQ to Standard Progressive Matrices/Colored Progressive Matrices IQ in each diagnostic group. For the 11 cases in which no direct cognitive testing was possible, 9 cases had Adaptive Behavior Composite on the VABS <20, and these cases were assigned an IQ score of 19 to reflect their profound level of mental retardation; two cases had no VABS data and were excluded from analysis involving IQ. The (weighted) mean (SD) FSIQ of the total ASD sample was 69.4 (24.1) and the range was 19 to 136. Fifty-five percent of all children with an ASD and 73% of the most narrowly defined autism cases had IQs <70 (Baird et al., 2006).

Parents completed the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Each subscale has five questions that are rated not true, somewhat true, and certainly true and scores 0 to 2 with higher scores indicating higher pathology. A total problem score derived from the hyperactivity/inattention, conduct problems, and emotional problems subscale scores was used in the present analysis. Information on parental education was also collected (defined by the highest academic qualification of either parent: 0 = none, 1 = O level [school-leaving examination given at age 16 years], 2 = NVQ [technical qualification], 3 = A level [school-leaving examination given at age 18 years], 4 = graduate, 5 = postgraduate).

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Low-Risk School and General Population Samples

School Sample. The SCQ was sent to 936 families with children attending mainstream schools in a predominantly middle-income town in the southeastern United Kingdom. An initial mailing was followed by a reminder letter. A total of 411 SCQs were returned (rate 43.9%). The mean age of the children was 12.0 years (SD 0.3), and none had a Statement of Special Educational Needs.

General Population Sample. Children were recruited from one postal district in a mixed low- to middle-income town on the southern coast of the United Kingdom. Every family with a child born within an 18-month cohort was sent the SCQ (n = 582). An initial mailing was followed by a mailed reminder, then a telephone call, and then a home visit. A total of 247 SCQs were returned for a response rate of 42.4%. The mean age of children was 11.5 (SD 0.6). Sixteen (6.5%) parents reported their child as having a Statement of Special Educational Needs.

Statistical Analysis

SNAP Sample. Stratification of the ASD/SEN sample was based on whether a child had a locally recorded ASD diagnosis (yes/no) and four levels of SCQ score (low score [<8], moderately low score [8–14], moderately high score [15–21], high score [>22]; see Baird et al., 2006 and Figure 1 for details). Use of weights allowed all statistics such as proportions, means, group differences, and screen performance measures to be presented as target population estimates, taking account not only of the differences in sampling proportions according to SCQ score and local ASD diagnosis but also the differential response to the SCQ associated with a prior local ASD diagnosis, health district, and child's sex. Wald test statistics (adjusted t and F tests) and p values were calculated using the linearization version of the robust parameter covariance matrix as implemented by the svy procedures of Stata 9 (Stata Corporation, 2005). Confidence intervals for signal detection statistics such as sensitivity (Se), which compare the screen with a gold standard, or area under the curve (AUC), which compare the screen with another test measure, were obtained by bootstrap resampling. Statistics presented for the school and general population samples are unweighted because no stratified sampling was performed.

RESULTS

SNAP Sample

The mean SCQ score in the at-risk sample was 15.2 (SD 8.6) and the sample scored across nearly the full range of the possible scores (0–39). Figure 2 shows the distribution of SCQ scores for the 255 cases seen for a research diagnostic assessment, stacked by consensus diagnosis. The bimodal distribution is due to the stratified sample design of the prevalence study (see Baird et al., 2006 for details). Figure 2 shows exact frequencies; however, all of the subsequent analyses on the at-risk sample are weighted to take the sampling proportions and differential response into account.

The weighted mean (SD) SCQ scores for non-ASD, other ASD, and childhood autism cases were 10.8 (± 6.1), 19.6 (± 6.6), and 26.6 (± 4.4), respectively. SCQ scores were highly correlated with ASD symptom severity as measured by the ADI-R (total algorithm score: r = 0.79, p < .001) and consensus *ICD-10* symptom count (r = 0.71, p < .001), although more moderately correlated with ADOS total algorithm score (r = 0.42, p < .001). SCQ scores were moderately negatively correlated with VABS composite scores (r = −0.38,

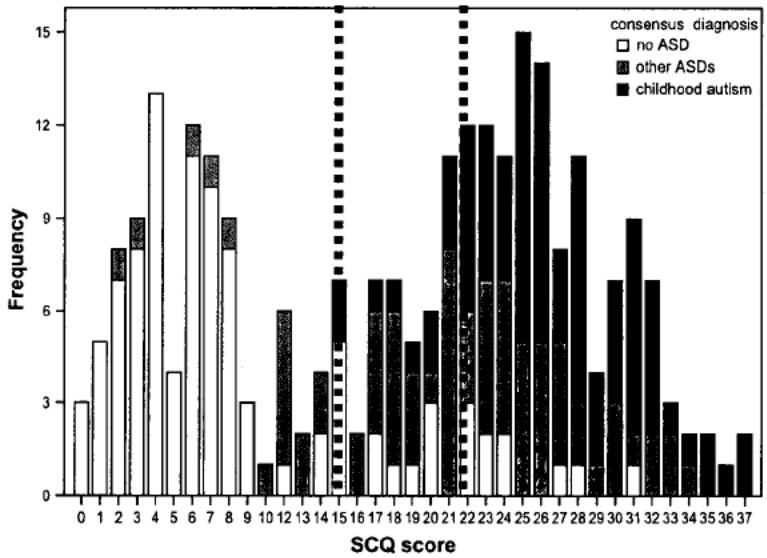

Fig. 2 Distribution of SCQ scores in the SNAP sample by consensus diagnosis (showing cutpoints of 15 and 22). SCQ = Social Communication Questionnaire; SNAP = Special Needs and Autism Project. ASD = autism spectrum disorder.

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$p < .001$) but the correlation between SCQ scores and IQ was negligible ($r = -0.05$, not significant).

Discrimination Between ASD and Non-ASD Cases in the At-Risk SNAP Sample

A receiver operating characteristic (ROC) analysis was performed to assess the discriminant power of the SCQ in distinguishing ASDs (including autism) cases from non-ASD cases (Dunn, 2000; Hanley and McNeil, 1982). The AUC was 0.88 (95% CI 0.82–0.93), indicating strong discriminant ability. At the recommended cutoff of ≥15, Se was 0.88 (95% CI 0.78–0.95), specificity (Sp) 0.72 (95% CI 0.57–0.85), positive predictive value was 0.64 (95% CI 0.50–0.78), and negative predictive value was 0.91 (95% CI 0.82–0.97). To determine whether the ability of the SCQ to discriminate between ASD and non-ASD cases varied depending on IQ or parental education, the ROC analysis was repeated for cases with low (FSIQ <70) versus high (FSIQ >70) IQ and high (3–5) versus low (0–2) parental education. The AUC was ≥0.87 for both of these subgroup comparisons. Figure 3 shows the ROC curves for the SCQ (with labels for each score between 0 and 39) compared to that for the ADI-R total algorithm score. The AUC was high for both instruments.

Child and family characteristics relevant to being a true case missed by the cutpoint (i.e., being a false negative [FN] compared to being a true positive [TP]) and to being a noncase falsely identified by the cutpoint (i.e., being a false positive [FP] compared to being a true negative [TN]) were examined. We considered that

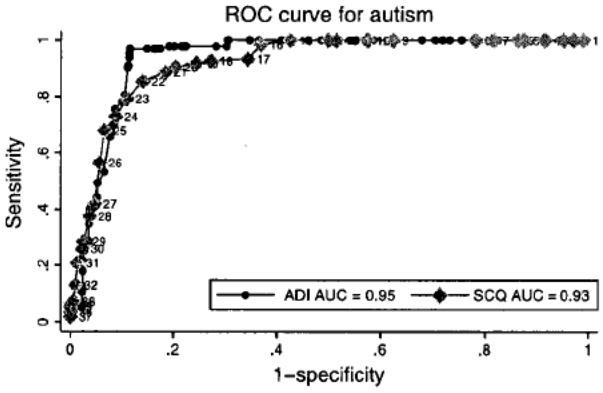

Fig. 3 ROC curve for SCQ and ADI-R discriminating ASD versus non-ASD (≥15). ROC = receiver operating characteristic; SCQ = Social Communication Questionnaire; ADI-R = Autism Diagnostic Interview-Revised; ASD = autism spectrum disorder.

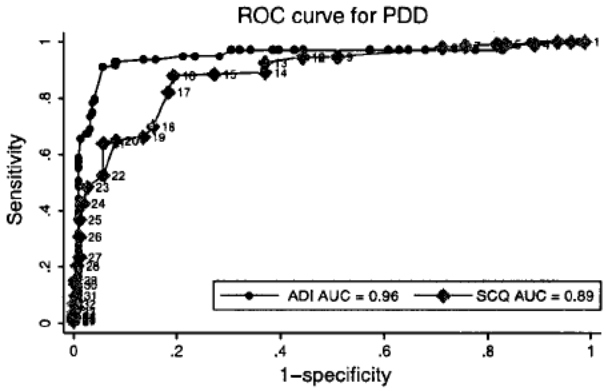

Fig. 4 ROC curve for SCQ and ADI-R discriminating autism vs. nonautism (≥22). ROC = receiver operating characteristic; SCQ = Social Communication Questionnaire; ADI-R = Autism Diagnostic Interview-Revised.

IQ, total algorithm scores on the ADI-R and ADOS-G, *ICD-10* total symptom count, and SDQ total problem score were relevant child characteristics and that parental education was a relevant background variable that may influence screen performance. FN cases had lower ADI-R algorithm scores (mean, 32.2, SE 3.13) than TP cases (40.9 ± 2.2; $Z = 1.98$; $p < .05$). FP cases had higher ADI-R algorithm scores (20.3 ± 1.6 versus 8.5 ± 1.0; $Z = 3.05$; $p < .01$) and higher SDQ total problem scores (14.3 ± 2.2 versus 12.1 ± 0.8; $Z = 2.06$; $p < .05$) than TN cases. FP cases did show a moderate level of ASD symptoms with a mean (SE) *ICD-10* total symptom score of 3.2 ± 0.5. Only 1.2% had received an ASD diagnosis from their local teams, however. All were given a non-ASD *ICD-10* diagnosis following assessment in the following (weighted) proportions: learning disability/mental retardation, 61.6%; language disorder, 7.7%; hyperkinetic disorder/ADHD, 25.2%; and other medical conditions, 5.5%.

Discrimination of Autism Cases From Nonautism Cases in the At-Risk SNAP Sample

A further ROC analysis, examining the ability of the SCQ to differentiate between childhood autism and nonchildhood autism cases (combining the other ASD and non-ASD groups) at the recommended cutoff of ≥22 also indicated strong discrimination (AUC 0.93, 95% CI 0.90–0.96), Se = 0.90 (95% CI 0.83–0.96); Sp = 0.86 (95% CI 0.80–0.90), PPV = 0.47 (95% CI 0.36–0.57), NPV = 0.98 (95% CI 0.97–0.99)). For the high and low IQ and high and low parental education subgroups, all of the AUCs were ≥0.90. Figure 4 shows

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the ROC curves for the SCQ and ADI-R, and, once again, the AUC was high for both instruments.

There were no differences between FN and TP cases in IQ, ADI-R, and ADOS-G algorithm scores, *ICD-10* total symptom count, total SDQ score or parental education. FP cases (38.9 ± 2.0) had higher ADI-R algorithm scores than TNs (14.6 ± 1.5; $Z = 6.02$; $p < .001$). FP cases showed a high level of ASD symptoms with a mean (SE) *ICD-10* total symptom score of 5.6 ± 0.4, although the clinical consensus diagnosis for these cases was not childhood autism. Of the cases, 21.4% had received an ASD diagnosis from their local teams, although 70.6% of the FPs at the cutpoint of 22 received a consensus diagnosis of other ASDs. All of the other FPs were given a non-ASD *ICD-10* diagnosis following assessment in the following (weighted) proportions: learning disability/mental retardation, 52.0%; language disorder, 27.8%; hearing impairment, 4.7%; hyperkinetic disorder/ADHD, 14.3%; and other medical conditions, 1.1%.

Distribution of SCQ Scores in the Low-Risk School and General Population Samples

The distribution of SCQ scores in the school and general population samples was strongly negatively skewed. The mean (SD) SCQ score for the school sample was 4.1 ± 4.7, and the mean SCQ score for the general population cohort was 4.7 ± 5.0.

Of the school sample, 4.4% obtained an SCQ score of ≥15. The majority of these cases (16/18, 88.9%) had a neurodevelopmental diagnosis recorded (e.g., intellectual disability/mental retardation, language disorder, ADHD), although only 2 of 18 (11.1%) cases scoring at or above 15 had an ASD diagnosis recorded locally. Six cases scored at or above 22 and one (16.7%) of these had an ASD diagnosis recorded locally. The five others had other neurodevelopmental diagnoses recorded locally.

Of the general population sample, 5.3%scored at 15 or above on the SCQ. Twelve of 13 (92.3%) of these cases had a neurodevelopmental diagnosis recorded locally, of which seven of 13 (53.8%) of cases had an ASD diagnosis recorded locally. Four (of 13) cases scored at or above 22, and each had an ASD diagnosis recorded locally.

There was one FN among the school sample based on locally recorded diagnosis; this child has an SCQ score of 7. There were two FN cases within the general population cohort based on locally recorded diagnosis; one had an SCQ score of 9, and the other had an SCQ score of 12.

DISCUSSION

Properties of the SCQ in the At-Risk SNAP Sample

In the population-weighted SNAP sample, the SCQ discriminated well between children with and without ASD at the established cutpoint of ≥15. The Se (0.88) and Sp (0.72) were similar to that in the initial validation study (Se = 0.85; Sp = 0.75; Berument et al., 1999) and also compare well with those of two other recently published screening instruments for ASD (Social and Communication Disorders Checklist: Se = 0.90, Sp = 0.69 [Skuse et al., 2005]; Social Responsiveness Scale: Se = 0.85, Sp = 0.75 [Constantino and Gruber, 2005]). Two recent studies used the SCQ in younger samples of 3- to 6-year-old children and found reduced Se (0.71) in one study (Eaves et al., 2006a) and reduced Sp (0.54) in the other (Allen et al., in press; Eaves et al., 2006b). Reduced sensitivity in a younger sample is consistent with the fact that not all autism symptoms inquired about on the SCQ will necessarily have emerged in 3-year-olds with an ASD (e.g., repetitive routines or imaginative games with peers [Charman et al., 2005; Cox et al., 1999]) or not sufficiently for parents to have identified them as noteworthy.

When discriminating between autism and nonautism cases (including other ASDs) at the cutpoint of ≥22, the Se (0.90) and Sp (0.86) remained high. Note that these figures cannot be directly compared to those reported in Berument et al. (1999), who used the cutpoint of 22 to discriminate between autism and other ASD cases. We report data for the autism versus nonautism (including cases with an ASD but not a childhood autism diagnosis) discrimination because this is more likely to reflect the use of the screen in clinical practice, in which a sample will likely consist of children with autism, children with other ASDs, and children who do not have an ASD. The ROC analysis showed that the SCQ discriminated between ASD and non-ASD a little less well and autism and nonautism cases almost as well as the ADI-R. For diagnostic assessment, a full parental interview regarding current and past development and behavior and structured observation of the child, preferably including a

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peer-group setting, are essential. Our study demonstrates that for some clinical and research purposes, the SCQ can be an efficient first-level screen to identify children with likely ASD or autism.

At both cutpoints Se and Sp in this sample were similar for the high and the low IQ subgroups and the correlation between SCQ score and IQ was close to zero. This contrasts with the study by Eaves et al. (2006b) who reported that SCQ scores were negatively correlated with IQ. Similarly, the ability of the SCQ to discriminate case and noncases at both cutpoints did not differ according to parental education. In different samples FP and FN cases may be explained by different child (e.g., IQ, age) and family (e.g., parental knowledge about autism, recognition of symptoms) factors, and these need to be considered alongside the score on the SCQ when assessing whether a child may likely have an ASD.

As would be expected, screen FNs scored lower than screen TPs, and, conversely, FPs scored higher than TNs on the ADI-R. The questions on the SCQ were closely modeled on ADI-R items, and on both instruments parents are the respondents. In contrast to Berument et al. (1999), in our study, parents completed the SCQ before completion of the ADI-R, thus reducing response bias on the screening instrument (note that the diagnosis relied on global clinical consensus using all information and not just the ADI-R). FPs at both cutpoints also had higher *ICD-10* total symptom scores than TNs (although lower scores than the screen TPs), reflecting the fact that many of the FP cases identified by the screen had subthreshold levels of ASD symptomatology. The majority of the FPs (~70%) at the cutpoint of 22 , which identifies likely autism cases, had a study consensus diagnosis of ASD; however, only one fifth had an ASD diagnosis from their local clinical team and few of the FPs at the cutpoint of 15 did so. One finding from the SNAP study was that only 58% of cases meeting consensus diagnosis of childhood autism had received an ASD from their local clinical teams, and this rate fell to 23% of cases meeting consensus diagnosis for other ASDs (Baird et al., 2006). Thus, reliance on local clinical diagnosis as the gold standard would underestimate the true proportion with ASDs among the FPs at the autism cutoff.

Screen FPs (in the ASD versus non-ASD comparison) scored higher than screen TNs on the total problem score of the SDQ. In response to questions on the SCQ that are meant to be measuring autism symptoms, some parents may rate their child's emotional, hyperactivity, or conduct difficulties. One previous study has reported high scores on the SCQ for children with mood and anxiety disorder in whom a clinical diagnosis of PDD had been excluded (Towbin et al., 2005). Among FPs at both cutpoints, we found children meeting criteria for other *ICD-10* neurodevelopmental conditions, including intellectual and learning disabilities, language delay, hearing impairment, hyperkinesis/ADHD, and physical disability.

Properties of the SCQ in the School and General Population Samples

Similar to the findings with other screens in normal populations (Constantino and Todd, 2003; Posserud et al., 2006; Skuse et al., 2005), the distribution of SCQ scores in the school and general population was heavily skewed to low scores, and the distribution of scores was continuous. In both samples approximately 4% to 5% of children scored above the SCQ cutoff of 15 that discriminated well between children with and without ASD. Not all of these screen-positive children had received a local clinical ASD diagnosis: 11% in the school sample and 54% in the general population sample. In both samples approximately 1.5% of children scored above the SCQ cutoff of 22 that discriminated well between children with and without childhood autism. Half of these children had received a local clinical ASD diagnosis. If the findings of local underidentification of ASD from the SNAP study apply to these samples from the same geographic region, then these may be underestimates of the number of actual cases of ASD in those who scored above the SCQ thresholds for ASD and autism (Baird et al., 2006). In both low-risk samples children with a locally recorded ASD diagnosis were rarely screen negative (<0.5% SCQ <15), although here local underidentification may underestimate the rate of FNs; however, almost all children with an SCQ score of ≥15 (~90%) had ASD or another neurodevelopmental disorder, including learning difficulties, language delay, and hyperkinetic disorder/ADHD.

Strengths

The strengths of the present study include the generalizability of the findings due to the population-weighting

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procedure, the calculation of CIs around the instrument parameter estimates, the inclusion of children only in the sample (compared to Berument et al., 1999), and the inclusion of both low and high IQ children (compared to Skuse et al., 2005). The comprehensive diagnostic assessment and use of a clinical consensus decision-making process that was corroborated by independent expert rating (see Baird et al., 2006) are also strengths. We were also able to test whether child or family characteristics systematically related to FP and FN identification. Although the two studies investigating how the SCQ worked in unselected samples of same-age children were less methodologically rigorous, the present samples of children compare well in terms of size to other published studies (n = 411 and n = 247, respectively, compared with n = 118 in Skuse et al., 2005).

Limitations

One limitation of the present study is that the age of the at-risk sample at the time of screening (9–10 years) is older than would be required for first-level screening of young children, although it is still an age at which many children are referred for possible ASD. Other studies have begun to investigate how well the SCQ works in preschool children, so far with mixed findings (Eaves et al., 2006a,b). In comparison to our assessment of the SCQ in the at-risk SNAP sample, our attempt to screen children in the two low-risk samples had limitations: local clinical diagnoses of the unselected population subsamples were not confirmed by direct or standard clinical assessment and uptake was moderate only and subject to (unknown) bias, reducing the generalizability of these findings. They were considered worthwhile, however, because nothing was known about how the SCQ performs outside clinical samples, and screening instrument properties vary with sample prevalence and characteristics (Clark and Harrington, 1999).

Clinical Implications

This study confirms the utility of the SCQ as a first-level screen for ASD in at-risk samples of school-age children. In both our at-risk SNAP sample and in the low-risk general population samples, scoring above the cutoffs for autism (22) or ASD (15) was highly indicative that the child had childhood autism or ASD, respectively, or another neurodevelopmental condition that would warrant further assessment and likely support and intervention.

Disclosure: Prof. Baird has served as an occasional expert witness for the diagnosis of autism. Prof. Pickles receives royalties from SCQ and ADOS-G instruments. The other authors have no financial relationships to disclose.

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Psychological Functioning and Coping Among Mothers of Children With Autism: A Population-Based Study Guillermo Montes, PhD, Jill S. Halterman, MD, MPH

Objectives: Studies suggest that having a child with autism has a negative impact on maternal psychological functioning, but no large-scale, population-based studies are available. The objectives of this study were to (1) describe the psychological functioning, physical and mental health, family communication, and parenting support of mothers of a child with autism compared with other mothers on a population basis and (2) assess the independent relationship between having a child with autism and these outcomes, controlling for the child's social skills and demographic background. *Methods:* Mothers of 61,772 children who were 4 to 17 years of age were surveyed by the National Survey of Children's Health, 2003. Autism was measured from an affirmative maternal response to the question, "Has a doctor or health professional ever told you your child has autism?" There were 364 children with autism in the sample. *Results:* Mothers of a child with autism were highly stressed and more likely to report poor or fair mental health than mothers in the general population, even after adjustment for the child's social skills and demographic background. However, mothers of a child with autism were more likely to report a close relationship and better coping with parenting tasks and less likely to report being angry with their child after adjustment for the child's social skills and demographic background. Having a child with autism was not associated with lower social support for parenting, an altered manner in which serious disagreements were discussed in the household, or increased violence in the household. *Conclusions:* Mothers of children with autism showed remarkable strengths in the parent–child relationship, social support, and stability of the household in the context of high stress and poorer mental health. **Pediatrics** 2007:119:e1040–e1046.

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Efficacy of three screening instruments in the identification of autistic-spectrum disorders

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Background Screening instruments for autistic-spectrum disorders have not been compared in the same sample.

Aims To compare the Social Communication Questionnaire (SCQ), the Social Responsiveness Scale (SRS) and the Children's Communication Checklist (CCC).

Method Screen and diagnostic assessments on 119 children between 9 and 13 years of age with special educational needs with and without autistic-spectrum disorders were weighted to estimate screen characteristics for a realistic target population.

Results The SCQ performed best (area under receiver operating characteristic curve (AUC)=0.90; sensitivity 0.86; specificity 0.78). The SRS had a lower AUC (0.77) with high sensitivity (0.78) and moderate specificity (0.67). The CCC had a high sensitivity but lower specificity (AUC=0.79; sensitivity 0.93; specificity 0.46). The AUC of the SRS and CCC was lower for children with IQ < 70. Behaviour problems reduced specificity for all three instruments.

Conclusions The SCQ, SRS and CCC showed strong to moderate ability to identify autistic-spectrum disorder in this at-risk sample of school-age children with special educational needs.

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There is considerable interest in screening instruments that identify children with possible autistic-spectrum disorders for a more in-depth diagnostic assessment. Recently developed screening instruments that have demonstrated promising properties in initial validation studies include the Social Communication Questionnaire (SCQ; sensitivity 0.85; specificity 0.75; Berument *et al*, 1999) and the Social Responsiveness Scale (SRS; 0.85; 0.75; Constantino & Gruber, 2005). The Children's Communication Checklist (CCC; Bishop, 1998) has a pragmatic composite sub-scale that has been shown to discriminate well between individuals with and without autism (Bishop & Baird, 2001). For clinicians and researchers a key consideration is which screen is most appropriate to their service or study. In the present study we directly compared the instrument properties of the SCQ, SRS and CCC in identifying individuals with autistic-spectrum disorders in a subsample of the Special Needs and Autism Project (SNAP; Baird *et al*, 2006) cohort of children 9–13 years of age with special educational needs with and without autistic-spectrum disorders.

METHOD

The study was approved by the South East Multicentre Research Ethics Committee (00/01/50). Patients gave informed consent.

Screening instruments

Social Communication Questionnaire

The SCQ (Rutter *et al*, 2003) is a 40-item parent-report questionnaire that asks about characteristic autistic behaviour. Each item is scored 0 or 1, with 1 being the score for endorsement of each symptom of autism. Total scores can range from 0 to 39 (the first item is a language screening question that is not included in the total score). The questionnaire is based on the Autism Diagnostic Interview – Revised (ADI–R; Lord *et al*, 1994) and it has established validity for a diagnosis of autism (Berument *et al*, 1999). Nineteen items rate current behaviour and 20 rate behaviour when the child was 4–5 years old. The recommended cut-off score for autistic-spectrum disorder or pervasive developmental disorder is $\geqslant 15$.

Social Responsiveness Scale

The SRS (Constantino & Gruber, 2005) is a 65-item rating scale asking about characteristic autistic behaviour over the previous 6 months. Each item is scored from 0 ('never true') to 3 ('almost always true'). Total scores can range from 0 to 195. For the present analysis a cut-off score of $\geqslant 75$ was chosen as that which best discriminates children with and without autistic-spectrum disorders (Constantino & Gruber, 2005: p. 38). Scores on the SRS discriminate between children with and without autistic-spectrum disorders and are strongly correlated with ADI–R domain scores (r=0.65–0.77; Constantino *et al*, 2003).

Children's Communication Checklist

Although not developed as a screen for autistic-spectrum disorders, the CCC (Bishop, 1998) is a 70-item rating scale that asks about language and communication impairments. Each item is scored 0 ('does not apply'), 1 ('applies somewhat'), 2 ('definitely applies') or missing value ('unable to judge'). Items ask about language and communication impairments and about competencies. The CCC is divided into 9 sub-scales: two sub-scales assess aspects of language structure (syntax and speech); two assess aspects of autistic behaviour (social relationships and interests); and five assess aspects of pragmatic communication (inappropriate initiation, coherence, stereotyped conversation, use of context, and rapport). These last five scales can be combined into a pragmatic composite. Bishop (1998) found that a CCC pragmatic composite score $\leqslant 132$ best identified children with pragmatic language impairment. This cut-off also discriminated well between children with and without autism in a clinical sample, but less well between individuals with Asperger syndrome or pervasive developmental disorder, not otherwise specified (PDD–NOS) and those with attention-deficit hyperactivity disorder (ADHD) (Bishop & Baird, 2001). The present study was started before the publication of the Children's Communication Checklist – Version 2 (CCC–2; Bishop, 2003).

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SNAP cohort

As part of the larger SNAP study of the prevalence of autistic-spectrum disorders (Baird *et al*, 2006), within a total population cohort of 56 946 children born between 1 July 1990 and 31 December 1991 all those with a current clinical diagnosis of pervasive developmental disorder (n=255) or considered at risk of having the undetected disorder by virtue of having a statement of special educational needs (n=1515) were screened using the SCQ. (In the UK a statement of special educational needs is a legal document issued by a local educational authority when children require significant additional support in school because they have learning and/or behavioural problems.) A total of 1066 SCQs were returned completed (return rate 60.2%); 31 families declined further participation, leaving 1035 (return rate 58.5%) who returned the SCQ and opted in for further assessments. Mean age at SCQ screening in the whole SNAP sample was 10.3 years (s.d.=0.4 years). We have previously reported on the screening properties of the SCQ in the total sample, finding similar discrimination between individuals with autistic-spectrum disorders and those without as in the original validation sample (sensitivity 0.88; specificity 0.72; Chandler *et al*, 2007).

A stratified subsample (by coincidence, also n=255) received a comprehensive diagnostic assessment, including standardised clinical observation (the Autism Diagnostic Observation Schedule – Generic (ADOS–G; Lord *et al*, 2000)), parent-interview assessments of autistic symptoms (ADI–R; Lord, *et al*, 1994), language and IQ tests, evaluation of psychiatric comorbidities and a medical examination. The team used ICD–10 research diagnostic criteria (World Health Organization, 1993) to derive a clinical consensus diagnosis of childhood autism, other autistic-spectrum disorders or no autistic-spectrum disorder (for details see Baird *et al*, 2006). For 36 randomly selected children, project consensus diagnoses were compared with diagnoses by eight internationally recognised experts using ICD–10 criteria (two experts independently rated the ADI–R, ADOS–G, psychometric findings and a clinical vignette for each case). Agreement between the project consensus and expert diagnoses was 93% with (weighted) κ=0.77 (for details see Baird *et al*, 2006: Fig. 1).

We collated the following data for our subsample of 119 children: IQ; severity of symptoms of autism, measured by ADI–R and ADOS–G algorithm total scores; a total count of ICD–10 symptoms (0–12), systematically completed as part of the diagnostic review process of every case; parent and teacher reports of emotional and behavioural problems; and adaptive behaviour, assessed using the Vineland Adaptive Behavior Scales (VABS; Sparrow *et al*, 1984). The children's (n=118) IQ was measured using the Wechsler Intelligence Scale for Children (WISC–III–UK; Wechsler, 1992). The (weighted) mean full-scale IQ of the sample was 73.4 (s.e.=1.6) and the range was 40–136; 56% (weighted) of the children had an IQ<70. One child could not complete the WISC–III–UK and their IQ was derived using Raven's Standard Progressive Matrices (Raven *et al*, 1990).

Parents of a subsample of children (n=119) completed both the SRS and the CCC in addition to the SCQ. This afforded us the opportunity to directly compare the instrument properties of the three screens in the same sample.

Parents and teachers of these 119 children also completed the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997, 2001). Each sub-scale has five questions that are rated 'not true', 'somewhat true' and 'certainly true' and score 0–2, with higher scores indicating greater pathology. Four sub-scales (emotional problems, peer problems, conduct problems and hyperactivity) are summed to create a total problem score (range 0–40). We considered children whose teacher-rated ($\geq$16) and/or parent-rated ($\geq$17) total problem score fell around the 10% percentile in UK norms for SDQ scores (Meltzer *et al*, 2000) to have a high rate of behaviour problems.

Order of completion of assessments

In the larger study (Baird *et al*, 2006) the SCQ was used as the initial screening instrument to identify cases for in-depth diagnostic assessment; therefore the SCQ was completed for all children before the diagnostic assessments. For our subsample of 119 children with data on all three screening instruments the mean age at SCQ screening was 10.2 years (s.e.=0.4 years; range 9.5–11). The CCC was completed by parents immediately before the diagnostic assessment (mean age of children=12.0 years (s.e.=0.1 years; range 9.8–13.9). The SRS was completed at a mean age of 12.6 years (s.e.=0.4 years; range 11.8–13.2): for 50 children this was in advance of, and for 69 this was following, the diagnostic assessment and completion of the CCC. Scores on the three screening instruments were not consulted during the consensus clinical diagnostic process (for details see Baird *et al*, 2006). The 119 children in our subsample differed from the remainder of the cohort (n=136) in terms of IQ (mean=78.5 (s.e.=1.8) *v.* 67.4 (s.e.=2.2); ANOVA $F(1,251)=15.0$, $P<0.001$) but not symptom severity or parental education.

Statistical analysis

Stratification of the sample with autistic-spectrum disorders and special educational needs was based on whether or not a child had a locally recorded autistic-spectrum disorder diagnosis (yes/no) and one of four levels of SCQ score (low: <8; moderately low: 8–14; moderately high: 15–21; high: >22; for details see Baird *et al*, 2006: Fig. 1). Weighting allowed all statistics such as means, group differences and screen performance measures to be presented as target population estimates, taking account not only of the differences in sampling proportions according to SCQ score and local diagnosis of autistic-spectrum disorder, but also the differential response to the SCQ associated with a prior local autistic-spectrum disorder diagnosis, health district and child's gender. Wald test statistics (adjusted t- and F-tests) and P-values were calculated using the linearisation version of the robust parameter covariance matrix as implemented by the *svy* procedures of Stata 9 (Stata, 2005). A receiver-operator-characteristic (ROC) area-under-the-curve (AUC) analysis was performed to assess and compare the discriminant power of the screening instruments in distinguishing children with autistic-spectrum disorders (including autism) from those without (Hanley & McNeil, 1982; Dunn, 2000). Application of the weights ensured that this comparison was fair despite the SCQ-stratified sample design. Confidence intervals for weighted AUC estimates and tests were obtained using the bootstrap resampling ROC procedures of Stata 9, reverse coded in the case of the CCC.

RESULTS

Thirty-three children received a clinical consensus diagnosis of childhood autism; 37 a clinical consensus diagnosis of other

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autistic-spectrum disorders (other-ASD); and 49 children did not meet clinical consensus diagnosis for autism or other autistic-spectrum disorders (non-ASD). Of the 37 children in the other-ASD group: 2 met ICD–10 criteria for atypical autism because of late onset; 2 met ICD–10 criteria for atypical autism because of an insufficient number of areas of abnormality; 29 met ICD–10 criteria for other pervasive developmental disorders because of sub-threshold symptomatology; 3 met ICD–10 criteria for 'pervasive developmental disorder, unspecified' because of lack of information (incomplete assessment, adopted children for whom early history was not available); and 1 met ICD–10 criteria for overactive disorder associated with mental retardation and stereotyped movements. Diagnoses for the 49 children in the non-ASD group included intellectual disability (DSM–IV–TR 'mental retardation'; American Psychiatric Association, 2000) and learning difficulties (n=27), language delay/disorder (n=7), hyperkinetic and/or conduct disorder (n=6) and a variety of other medical, sensory and developmental diagnoses (n=9).

Table 1 shows the weighted mean scores of the sample on the three screens by consensus diagnostic group. As would be expected, individuals in the childhood autism group scored higher than those in the other-ASD and non-ASD groups on the SCQ and SRS and lower on the (reverse-scored) CCC pragmatic composite. Similarly, the children in the other-ASD group scored higher than those in the non-ASD group on the SCQ and SRS and lower on the CCC pragmatic composite. For the SCQ all three group-by-group comparisons were significant (other-ASD $v.$ non-ASD: $F(1,118)=39.8$, $P<0.001$; childhood autism $v.$ non-ASD: $F(1,118)=186.4$, $P<0.001$; childhood autism $v.$ other-ASD: $F(1,118)=28.2$, $P<0.001$). For the SRS and CCC all three comparisons reached significance, except for the childhood autism $v.$ other-ASD comparison on the SRS (SRS: other-ASD $v.$ non-ASD: $F(1,118)=6.2$, $P<0.05$; childhood autism $v.$ non-ASD: $F(1,118)=38.7$, $P<0.001$; childhood autism $v.$ other-ASD: $F(1,118)=2.7$, $P=0.10$; CCC: other-ASD $v.$ non-ASD: $F(1,118)=13.2$, $P<0.001$; childhood autism $v.$ non-ASD: $F(1,118)=29.5$, $P<0.001$; childhood autism $v.$ other-ASD: $F(1,118)=5.3$, $P<0.05$).

Total scores on the three screening instruments were highly and significantly correlated (weighted correlation coefficients SCQ–SRS=0.68; SCQ–CCC=−0.66; SRS–CCC=−0.75, all $P<0.001$). Table 2 shows the correlations between total scores on the three screening instruments and scores on the eight other diagnostic assessment measures. All three screening instruments were more highly correlated with the ADI–R total score and ICD–10 symptom count than with the ADOS–G total score. The SCQ and SRS scores were unrelated to IQ, and scores on the CCC were only weakly related, with lower IQ being associated with poor pragmatic ability (r=0.20, $P<0.05$). All three screening instruments were unrelated to language ability as measured by the British Picture Vocabulary Scale (BPVS; Dunn *et al*, 1987). Scores on all three screens were also significantly associated with the adaptive behaviour composite of the VABS and with parent-completed, but less so with teacher-completed SDQs.

The AUC, sensitivity, specificity, positive and negative predictive values of the three screening instruments in predicting ASD versus non-ASD status are shown in Table 3 and the ROC curves are shown in Fig. 1. The SCQ had a higher AUC (0.90) than the SRS (0.77; P=0.05) and the CCC (0.79, P=0.05), reflecting both its high sensitivity (0.86) and specificity (0.78). The AUC of the SRS and CCC did not differ from one another (P=0.84). The SRS had high sensitivity (0.78) but only moderate specificity (0.67); whereas the CCC had a high sensitivity but a low specificity (0.93 and 0.46 respectively).

To examine whether the three screens performed differently in subsamples of children (children with low (<70) $v.$ high (≥70) IQ; children with $v.$ without parent- and/or teacher-rated borderline behavioural problems on the SDQ), AUC analyses were repeated for these subgroups. Note that these analyses should be treated with caution, as the confidence intervals for some of the parameters are wide, reflecting smaller subsamples. However, although the SCQ and CCC performed similarly in the subsample with low IQ as they did for the whole sample, the SRS had a lower AUC (0.67), reflecting its lower specificity (0.57). In the subsample with high IQ the AUC was similar for all three screens (SCQ=0.90; SRS=0.87; CCC=0.88). All three instruments showed lowered specificity in the subsample with elevated behavioural problems (SCQ=0.57; SRS=0.41; CCC=0.30).

Table 1 Scores on the three screening instruments by diagnostic group

	Non-ASD (n=49) Mean (s.e.)	Other-ASD (n=37) Mean (s.e.)	Childhood autism (n=33) Mean (s.e.)
SCQ	9.5 (1.1)	19.2 (1.1)	25.8 (0.5)
SRS	68.0 (6.2)	97.8 (10.2)	116.1 (4.6)
CCC	131.9 (2.7)	120.3 (1.8)	114.5 (1.8)

ASD, autistic-spectrum disorder; CCC, Children's Communication Checklist; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale.

Table 2 Correlations between total scores on the three screens and scores on other diagnostic assessment measures

Measure	SCQ	SRS	CCC
ADI–R (n=117)	0.83***	0.59***	−0.58***
ADOS–G (n=119)	0.45***	0.48***	−0.36***
ICD–10 symptom count (n=119)	0.72***	0.59***	−0.55***
IQ (n=118)	0.01	−0.09	0.20*
BPVS (n=118)	0.12	0.09	0.06
VABS (n=103)	−0.38***	−0.44***	0.43***
Parent SDQ (n=119)	0.57***	0.73***	−0.67***
Teacher SDQ (n=108)	0.34***	0.36***	−0.47***

BPVS, British Picture Vocabulary Scale; CCC, Children's Communication Checklist; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; SRS, Social Responsiveness Scale; VABS, Vineland Adaptive Behavior Scales.
**P<0.05; ***P<0.001.

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Table 3 Properties (weighted values) of the three screening instruments

	SCQ ASD cut-off ⩾15	SRS ASD cut-off ⩾75	CCC PC cut-off ⩽132
Whole sample (n=119)			
AUC (95% CI)	0.90 (0.81–0.96)	0.77 (0.61–0.90)	0.79 (0.64–0.91)
Sensitivity (95% CI)	0.86 (0.65–0.96)	0.78 (0.57–0.92)	0.93 (0.87–0.97)
Specificity (95% CI)	0.78 (0.60–0.93)	0.67 (0.46–0.84)	0.46 (0.28–0.68)
PPV (95% CI)	0.74 (0.56–0.92)	0.63 (0.46–0.82)	0.56 (0.41–0.75)
NPV (95% CI)	0.88 (0.72–0.97)	0.81 (0.61–0.94)	0.90 (0.81–0.96)
Low IQ (n=44)			
AUC (95% CI)	0.92 (0.74–0.99)	0.67 (0.38–0.93)	0.72 (0.47–0.92)
Sensitivity (95% CI)	0.97 (0.88–1.00)	0.78 (0.46–1.00)	0.99 (0.96–1.00)
Specificity (95% CI)	0.73 (0.42–0.99)	0.57 (0.29–0.84)	0.41 (0.14–0.70)
PPV (95% CI)	0.68 (0.38–0.98)	0.52 (0.29–0.78)	0.50 (0.27–0.75)
NPV (95% CI)	0.98 (0.89–1.00)	0.81 (0.44–1.00)	0.99 (0.91–1.0)
High IQ (n=75)			
AUC (95% CI)	0.90 (0.77–0.97)	0.87 (0.73–0.95)	0.88 (0.73–0.97)
Sensitivity (95% CI)	0.77 (0.51–0.94)	0.78 (0.61–0.91)	0.88 (0.76–0.96)
Specificity (95% CI)	0.85 (0.60–0.98)	0.80 (0.58–0.94)	0.53 (0.30–0.86)
PPV (95% CI)	0.83 (0.58–0.97)	0.78 (0.53–0.94)	0.63 (0.42–0.89)
NPV (95% CI)	0.80 (0.57–0.96)	0.80 (0.60–0.91)	0.83 (0.68–0.94)
Low SDQ (n=33)			
AUC (95% CI)	1.0 (0.99–1.00)	0.77 (0.42–0.94)	0.86 (0.67–0.98)
Sensitivity (95% CI)	0.87 (0.54–1.00)	0.57 (0.15–0.93)	0.94 (0.70–1.00)
Specificity (95% CI)	0.99 (0.96–1.00)	0.93 (0.76–1.00)	0.60 (0.34–0.90)
PPV (95% CI)	0.91 (0.61–1.00)	0.47 (0.00–1.00)	0.21 (0.05–0.57)
NPV (95% CI)	0.99 (0.95–1.00)	0.95 (0.87–0.99)	0.99 (0.95–1.0)
High SDQ (n=77)			
AUC (95% CI)	0.83 (0.66–0.92)	0.67 (0.44–0.87)	0.66 (0.42–0.87)
Sensitivity (95% CI)	0.86 (0.66–0.97)	0.80 (0.55–0.95)	0.95 (0.89–0.99)
Specificity (95% CI)	0.57 (0.29–0.87)	0.41 (0.15–0.71)	0.30 (0.09–0.66)
PPV (95% CI)	0.73 (0.52–0.91)	0.64 (0.43–0.82)	0.64 (0.45–0.83)
NPV (95% CI)	0.76 (0.37–0.95)	0.61 (0.24–0.93)	0.81 (0.52–0.95)

ASD, autistic spectrum disorder; AUC, area under the curve; CCC PC, Children's Communication Checklist, pragmatic composite; NPV, negative predictive value; PPV, positive predictive value; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; SRS, Social Responsiveness Scale.

DISCUSSION

Summary of the screening properties

The performance of the SCQ was similar to the that in initial validation study (sensitivity=0.85; specificity=0.75; Berument *et al*, 1999; Rutter *et al*, 2003) and somewhat better than in several more recent studies that have included younger children and have reported reduced sensitivity (0.71: Eaves *et al*, 2006*a*; 0.71: Corsello *et al*, 2007; 0.67: Lee *et al*, 2007) or reduced specificity (0.71: Eaves *et al*, 2006*b*; 0.58: Allen *et al*, 2007; 0.54: Corsello *et al*, 2007). The present study included only a restricted age range but in a large sample Corsello *et al* (2007: Table 3) found that the sensitivity of the SCQ increased with age, perhaps reflecting the emergence of the full range of autistic symptoms over time. This is supported by comparison of the mean SCQ scores for children with a diagnosis of childhood autism in the present (25.8) and previous studies. Although our figure is very similar to the 25.2 obtained in the Berument *et al* (1999) study it is higher than the 20.3 obtained in the Corsello *et al* (2007) study, which included children 2–16 years and also the 19.2 of the Eaves *et al* (2006*b*) study, which included children aged 2–6 years.

The SRS had a lower sensitivity in our sample than in the original validation study (0.85; Constantino & Gruber, 2005) and both the SRS and CCC had reduced specificity (0.57 and 0.41 respectively) in our subsample with low IQ. The increased specificity of the SCQ compared with that of the SRS and CCC might be due to its fuller coverage of the third autism symptom domain of restricted and repetitive behaviours and interests. All three screens showed high discrimination between children with IQ⩾70 in the ASD and non-ASD groups with AUC values between 0.87 and 0.90. The CCC had a high sensitivity but low specificity, reflecting its broader cut-off for 'pragmatic impairment', rather than autistic-spectrum disorder itself. For some purposes, for example screening out individuals who might have autistic-spectrum disorder when characterising a non-ASD comparison group in a research study, high sensitivity is prioritised and lower specificity does not bring costs, and on the basis of the present data the CCC could be used for such a purpose. Geurts *et al* (2004) found that the CCC discriminated well between children with autism, children with ADHD and typical controls (discriminant function classification 78% in Study 1; 77% in Study 2).

All three screening instruments had lower specificity in the subsample with elevated levels of behavioural problems as measured by the SDQ. It is likely that in response to questions on the instruments that are meant to measure symptoms of autism, some parents are endorsing items that reflect aspects of their child's emotional, hyperactivity or conduct difficulties. One previous study has reported high scores on the SCQ for children with mood and anxiety disorders in whom a clinical diagnosis of pervasive developmental disorder had been excluded (Towbin *et al*, 2005), although such disorders are unlikely to be common in our sample as they usually do not form a reason for special educational needs registration. In the Towbin *et al* study significantly more children fell above the autistic-spectrum disorder cut-off on the SRS and the Social Interaction Deviance Composite on the CCC-2 than above the cut-off for the disorder on the SCQ (Towbin *et al*, 2005: Fig. 1, p. 458).

In addition to the prevalence of autistic-spectrum disorders in any particular clinical setting or research study, the characteristics (e.g. clinical diagnosis, IQ, age) of those with and without the disorder, family factors (e.g. parental education, parental knowledge about autism) and methodological factors, including whether the screen was completed before or after diagnostic assessment, will also affect how a screening

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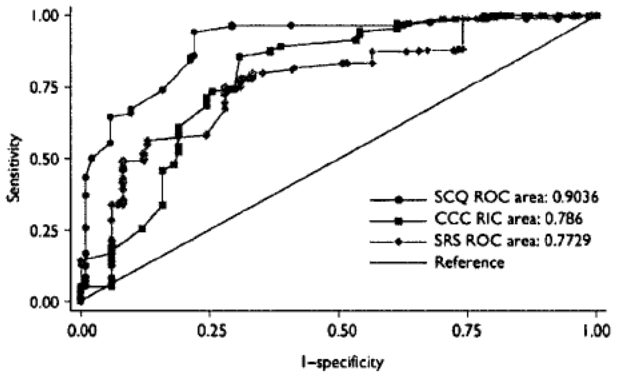

Fig. 1 Receiver operating characteristic (ROC) curves for the Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS) and Children's Communication Checklist (CCC).

instrument performs. Another factor that affects an instrument's performance in relation to a clinical diagnosis of autistic-spectrum disorder is the time period of the behaviour sampled and the three instruments used in this study differed in this respect. Whereas the CCC and SRS ask parents to rate current behaviour (for the SRS over the previous 6 months; unspecified for the CCC), about half of the items on the SCQ ask about behaviour in the 4- to 5-year period when symptoms of autism may be at their most prototypical. One further consideration that our study cannot address is whether screening instruments perform differently in different countries owing to cultural interpretation of the behaviours enquired about.

Example scenarios comparing use of the three screens

The meaning of statistics such as the AUC can be hard to translate into everyday examples to guide clinicians and researchers. To illustrate the potential impact of the different screen parameters on a hypothetical research study or clinical service we will outline two scenarios that summarise the consequences of choice of screening instrument. In both scenarios assume that among 250 children to be screened, 100 are 'true cases' of autistic-spectrum disorders and 150 are 'true non-cases'. Using estimates from the present analysis this translates into: the number of the 100 'true cases' that are screen positive (true positives) (SCQ=86; SRS=78; CCC pragmatic composite=93); the number of the 100 'true cases' that are screen negative (false negatives) (SCQ=14; SRS=22; CCC pragmatic composite=7); the number of the 150 true non-cases that are screen negative (true negatives) (SCQ=117; SRS=100.5; CCC pragmatic composite=69); and the number of the 150 true non-cases that are screen positive (false positives) (SCQ=33; SRS=49.5; CCC pragmatic composite=81). The relative importance of these figures depends on the purpose of using the screening instrument in a particular study/service.

In the first scenario, consider that the instruments is being used to estimate, for purely administrative reasons, the number of children within a special school system who have an autistic-spectrum disorder. That is, there is no consequence or cost (such as a follow-up assessment) attached to being screen positive. In this scenario, the estimated prevalence of autistic-spectrum disorder will vary by a factor of ~50%, depending on whether one is using the SCQ (119 screen positives, i.e. children with autistic-spectrum disorders identified), the SRS (127.5 identified) or the CCC pragmatic composite (173 identified), with the latter clearly overestimating the 'true' prevalence.

In a second scenario, consider a clinical service screening speech and language therapy referrals to identify children who should be 'fast tracked' into an expensive (and for parents sometimes anxiety provoking) multidisciplinary assessment. For this aim, high sensitivity is required for the screening procedure to be clinically useful. To maximise case-finding efficiency one could consider the proportion of cases correctly identified by the screen compared with cases missed by it (SCQ=6.14; SRS=3.55; CCC pragmatic composite=13.3). However, one would also want to minimise false positives in order not to use expensive assessment resource on children who do not have autistic-spectrum disorders and to avoid provoking unnecessary anxiety in parents. Here the most relevant figure is the number of false positives (SCQ=33; SRS=49.5; CCC pragmatic composite=81). In this scenario the SRS was least efficient in terms of case-finding and the CCC least cost-effective, with the SCQ performing best. Other scenarios would produce different outcomes, and the choice of which screen to use and which criterion to adopt could depend on the relative costs of false positives and false negatives – although these costs fall on different parties (false positives tend to cost services, whereas false negatives tend to cost the child and parent). Clinicians and researchers need to estimate as best they can the implications for their service/study of which screen they use for any particular purpose.

Strengths and limitations

The strengths of our study include: testing the ability of different screening instruments to identify children with autistic-spectrum disorders in the same sample; the generalisability of the findings, owing to the population-weighting procedure; the calculation of confidence intervals around the instrument parameter estimates; and the inclusion of both low- and high-IQ children. The comprehensive diagnostic assessment and use of a clinical consensus decision-making process that was corroborated by independent expert rating (see Baird *et al*, 2006) are also strengths. Furthermore, the screens were able to differentiate those with autistic-spectrum disorders from those without such disorders but with intellectual disability and language delay despite the considerable degree of symptom overlap between these conditions, especially in the area of impairments in communication.

One limitation of the study is that the age of the at-risk sample at the time of screening (9–13 years) is older than would be required for first-level screening of young children, although it is still an age at which many children are referred for possible autistic-spectrum disorders, in particular to child and adolescent mental health services (Skuse *et al*, 2005). Second, the SCQ was derived from items on the ADI–R and information from the ADI–R was part of the information used to achieve a clinical consensus diagnosis. This might explain, in part, the higher prediction of the SCQ compared with the SRS and CCC that we found. Another limitation is the

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relatively modest sample size, in particular when the subsamples with high/low IQ and high/low levels of behavioural problems were examined, leading to relatively wide confidence intervals. However, the sample size compares well with the majority of published data available on the SCQ, SRS and CCC.

Clinical implications

A score on a screening instrument is not a diagnosis. For diagnostic assessment a full parental interview regarding current and past development and behaviour, and structured observation of the child, preferably including a peer-group setting, is essential. Corsello *et al* (2007) found that the addition of information from the ADOS–G to information from the SCQ significantly improved specificity to detect autistic-spectrum disorders. For some clinical and research purposes they suggest that a multi-stage assessment beginning with the SCQ, followed by the ADOS–G and then including information from the time-intensive ADI–R assessment might be appropriate. Our study demonstrates that for some clinical and research purposes the SCQ, and to a lesser extent the SRS and CCC, can all be efficient first-level screening instruments for identifying children with possible autistic-spectrum disorder for a more in-depth assessment. Child characteristics such as IQ and behavioural problems affect performance of the screens, and this, in addition to considerations regarding the consequences/costs of a screen-positive or negative result, should be borne in mind when choosing which screen to use for any particular clinical or research purpose.

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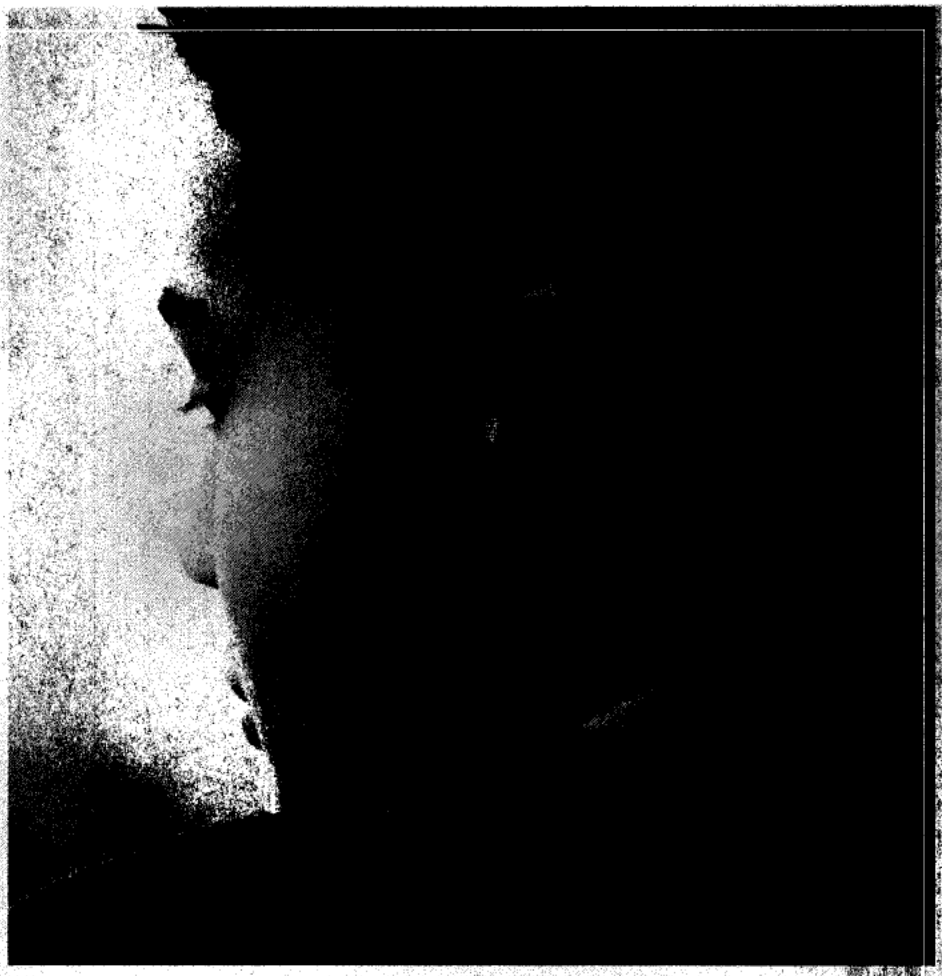

Autism Spectrum Disorders

DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTES OF HEALTH

NIMH National Institute of Mental Health

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Not until the middle of the twentieth century was there a name for a disorder that now appears to affect an estimated one of every five hundred children, a disorder that causes disruption in families and unfulfilled lives for many children. In 1943 Dr. Leo Kanner of the Johns Hopkins Hospital studied a group of 11 children and introduced the label *early infantile autism* into the English language. At the same time a German scientist, Dr. Hans Asperger, described a milder form of the disorder that became known as Asperger syndrome. Thus these two disorders were described and are today listed in the *Diagnostic and Statistical Manual of Mental Disorders* DSM-IV-TR (fourth edition, text revision)[1] as two of the five pervasive developmental disorders (PDD), more often referred to today as autism spectrum disorders (ASD). All these disorders are characterized by varying degrees of impairment in communication skills, social interactions, and restricted, repetitive and stereotyped patterns of behavior.

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The autism spectrum disorders can often be reliably detected by the age of 3 years, and in some cases as early as 18 months.[2] Studies suggest that many children eventually may be accurately identified by the age of 1 year or even younger. The appearance of any of the warning signs of ASD is reason to have a child evaluated by a professional specializing in these disorders.

Parents are usually the first to notice unusual behaviors in their child. In some cases, the baby seemed "different" from birth, unresponsive to people or focusing intently on one item for long periods of time. The first signs of an ASD can also appear in children who seem to have been developing normally. When an engaging, babbling toddler suddenly becomes silent, withdrawn, self-abusive, or indifferent to social overtures, something is wrong. Research has shown that parents are usually correct about noticing developmental problems, although they may not realize the specific nature or degree of the problem.

The pervasive developmental disorders, or autism spectrum disorders, range from a severe form, called autistic disorder, to a milder form, Asperger syndrome. If a child has symptoms of either of these disorders, but does not meet the specific criteria for either, the diagnosis is called pervasive developmental disorder not otherwise specified (PDD-NOS). Other rare, very severe disorders that are included in the autism spectrum disorders are Rett syndrome and childhood disintegrative disorder. This brochure will focus on classic autism, PDD-NOS, and Asperger syndrome, with brief descriptions of Rett syndrome and childhood disintegrative disorder on the following page.

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Rare Autism Spectrum Disorders

Rett Syndrome: Rett syndrome is relatively rare, affecting almost exclusively females, one out of 10,000 to 15,000. After a period of normal development, sometime between 6 and 18 months, autism-like symptoms begin to appear. The little girl's mental and social development regresses—she no longer responds to her parents and pulls away from any social contact. If she has been talking, she stops; she cannot control her feet; she wrings her hands. Some of the problems associated with Rett syndrome can be treated. Physical, occupational, and speech therapy can help with problems of coordination, movement, and speech.

Scientists sponsored by the National Institute of Child Health and Human Development have discovered that a mutation in the sequence of a single gene can cause Rett syndrome. This discovery may help doctors slow or stop the progress of the syndrome. It may also lead to methods of screening for Rett syndrome, thus enabling doctors to start treating these children much sooner, and improving the quality of life these children experience.*

Childhood Disintegrative Disorder: Very few children who have an autism spectrum disorder (ASD) diagnosis meet the criteria for childhood disintegrative disorder (CDD). An estimate based on four surveys of ASD found fewer than 2 children per 100,000 with ASD could be classified as having CDD. This suggests that CDD is a very rare form of ASD. It has a strong male preponderance.** Symptoms may appear by age 2, but the average age of onset is between 3 and 4 years. Until this time, the child has age-appropriate skills in communication and social relationships. The long period of normal development before regression helps differentiate CDD from Rett syndrome.

The loss of such skills as vocabulary are more dramatic in CDD than they are in classical autism. The diagnosis requires extensive and pronounced losses involving motor, language, and social skills.*** CDD is also accompanied by loss of bowel and bladder control and oftentimes seizures and a very low IQ.

* *Rett syndrome.* NIH Publication No. 01-4960. Rockville, MD: National Institute of Child Health and Human Development, 2001. Available at http://www.nichd.nih.gov/publications/pubskey.cfm?from=autism

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What Are the Autism Spectrum Disorders?

The autism spectrum disorders are more common in the pediatric population than are some better known disorders such as diabetes, spinal bifida, or Down syndrome.[2] Prevalence studies have been done in several states and also in the United Kingdom, Europe, and Asia. Prevalence estimates range from 2 to 6 per 1,000 children. This wide range of prevalence points to a need for earlier and more accurate screening for the symptoms of ASD. The earlier the disorder is diagnosed, the sooner the child can be helped through treatment interventions. Pediatricians, family physicians, daycare providers, teachers, and parents may initially dismiss signs of ASD, optimistically thinking the child is just a little slow and will "catch up." Although early intervention has a dramatic impact on reducing symptoms and increasing a child's ability to grow and learn new skills, it is estimated that *only 50% of children are diagnosed before kindergarten.*

All children with ASD demonstrate deficits in 1) social interaction, 2) verbal and nonverbal communication, and 3) repetitive behaviors or interests. In addition, they will often have unusual responses to sensory experiences, such as certain sounds or the way objects look. Each of these symptoms runs the gamut from mild to severe. They will present in each individual child differently. For instance, a child may have little trouble learning to read but exhibit extremely poor social interaction. Each child will display communication, social, and behavioral patterns that are individual but fit into the overall diagnosis of ASD.

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Children with ASD do not follow the typical patterns of child development. In some children, hints of future problems may be apparent from birth. In most cases, the problems in communication and social skills become more noticeable as the child lags further behind other children the same age. Some other children start off well enough. Oftentimes between 12 and 36 months old, the differences in the way they react to people and other unusual behaviors become apparent. Some parents report the change as being sudden, and that their children start to reject people, act strangely, and lose language and social skills they had previously acquired. In other cases, there is a "plateau," or leveling, of progress so that the difference between the child with autism and other children the same age becomes more noticeable.

ASD is defined by a certain set of behaviors that can range from the very mild to the severe. The following possible indicators of ASD were identified on the Public Health Training Network Webcast, *Autism Among Us*.[3]

Possible Indicators of Autism Spectrum Disorders

- Does not babble, point, or make meaningful gestures by 1 year of age
- Does not speak one word by 16 months
- Does not combine two words by 2 years.
- Does not respond to name
- Loses language or social skills

Some Other Indicators

- Poor eye contact
- Doesn't seem to know how to play with toys

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- Excessively lines up toys or other objects
- Is attached to one particular toy or object
- Doesn't smile
- At times seems to be hearing impaired

Social Symptoms

From the start, typically developing infants are social beings. Early in life, they gaze at people, turn toward voices, grasp a finger, and even smile.

In contrast, most children with ASD seem to have tremendous difficulty learning to engage in the give-and-take of everyday human interaction. Even in the first few months of life, many do not interact and they avoid eye contact. They seem indifferent to other people, and often seem to prefer being alone. They may resist attention or passively accept hugs and cuddling. Later, they seldom seek comfort or respond to parents' displays of anger or affection in a typical way. Research has suggested that although children with ASD are attached to their parents, their expression of this attachment is unusual and difficult to "read." To parents, it may seem as if their child is not attached at all Parents who looked forward to the joys of cuddling, teaching, and playing with their child may feel crushed by this lack of the expected and typical attachment behavior.

Children with ASD also are slower in learning to interpret what others are thinking and feeling. Subtle social cues—whether a smile, a wink, or a grimace—may have little meaning. To a child who misses these cues, "Come here" always means the same thing, whether the speaker is smiling and extending her arms for a hug or frowning and planting her fists on her hips. Without the ability to

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interpret gestures and facial expressions, the social world may seem bewildering.

To compound the problem, people with ASD have difficulty seeing things from another person's perspective. Most 5-year-olds understand that other people have different information, feelings, and goals than they have. A person with ASD may lack such understanding. This inability leaves them unable to predict or understand other people's actions.

Although not universal, it is common for people with ASD also to have difficulty regulating their emotions. This can take the form of "immature" behavior such as crying in class or verbal outbursts that seem inappropriate to those around them. The individual with ASD might also be disruptive and physically aggressive at times, making social relationships still more difficult. They have a tendency to "lose control," particularly when they're in a strange or overwhelming environment, or when angry and frustrated. They may at times break things, attack others, or hurt themselves. In their frustration, some bang their heads, pull their hair, or bite their arms.

Communication Difficulties

By age 3, most children have passed predictable milestones on the path to learning language; one of the earliest is babbling. By the first birthday, a typical toddler says words, turns when he hears his name, points when he wants a toy, and when offered something distasteful, makes it clear that the answer is "no."

Some children diagnosed with ASD remain mute throughout their lives. Some infants who later show signs of ASD coo and babble during the first few months of life, but they soon stop. Others may be delayed, developing language as late as age 5 to 9.

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Some children may learn to use communication systems such as pictures or sign language.

Those who do speak often use language in unusual ways. They seem unable to combine words into meaningful sentences. Some speak only single words, while others repeat the same phrase over and over. Some ASD children parrot what they hear, a condition called *echolalia*. Although many children with no ASD go through a stage where they repeat what they hear, it normally passes by the time they are 3.

Some children only mildly affected may exhibit slight delays in language, or even seem to have precocious language and unusually large vocabularies, but have great difficulty in sustaining a conversation. The "give and take" of normal conversation is hard for them, although they often carry on a monologue on a favorite subject, giving no one else an opportunity to comment. Another difficulty is often the inability to understand body language, tone of voice, or "phrases of speech." They might interpret a sarcastic expression such as "Oh, that's just great" as meaning it really IS great.

While it can be hard to understand what ASD children are saying, their body language is also difficult to understand. Facial expressions, movements, and gestures rarely match what they are saying. Also, their tone of voice fails to reflect their feelings. A high-pitched, sing-song, or flat, robot-like voice is common. Some children with relatively good language skills speak like little adults, failing to pick up on the "kid-speak" that is common in their peers.

Without meaningful gestures or the language to ask for things, people with ASD are at a loss to let others know what they need. As a result, they may simply scream or grab what they want. Until they are taught better ways to express their needs, ASD

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children do whatever they can to get through to others. As people with ASD grow up, they can become increasingly aware of their difficulties in understanding others and in being understood. As a result they may become anxious or depressed.

Repetitive Behaviors

Although children with ASD usually appear physically normal and have good muscle control, odd repetitive motions may set them off from other children. These behaviors might be extreme and highly apparent or more subtle. Some children and older individuals spend a lot of time repeatedly flapping their arms or walking on their toes. Some suddenly freeze in position.

As children, they might spend hours lining up their cars and trains in a certain way, rather than using them for pretend play. If someone accidentally moves one of the toys, the child may be tremendously upset. ASD children need, and demand, absolute consistency in their environment. A slight change in any routine—in mealtimes, dressing, taking a bath, going to school at a certain time and by the same route—can be extremely disturbing. Perhaps order and sameness lend some stability in a world of confusion.

Repetitive behavior sometimes takes the form of a persistent, intense preoccupation. For example, the child might be obsessed with learning all about vacuum cleaners, train schedules, or lighthouses. Often there is great interest in numbers, symbols, or science topics.

Problems that May Accompany ASD

Sensory problems. When children's perceptions are accurate, they can learn from what they see, feel, or hear. On the

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other hand, if sensory information is faulty, the child's experiences of the world can be confusing. Many ASD children are highly attuned or even painfully sensitive to certain sounds, textures, tastes, and smells. Some children find the feel of clothes touching their skin almost unbearable. Some sounds—a vacuum cleaner, a ringing telephone, a sudden storm, even the sound of waves lapping the shoreline—will cause these children to cover their ears and scream.

In ASD, the brain seems unable to balance the senses appropriately. Some ASD children are oblivious to extreme cold or pain. An ASD child may fall and break an arm, yet never cry. Another may bash his head against a wall and not wince, but a light touch may make the child scream with alarm.

Mental retardation. Many children with ASD have some degree of mental impairment. When tested, some areas of ability may be normal, while others may be especially weak. For example, a child with ASD may do well on the parts of the test that measure visual skills but earn low scores on the language subtests.

Seizures. One in four children with ASD develops seizures, often starting either in early childhood or adolescence.[4] Seizures, caused by abnormal electrical activity in the brain, can produce a temporary loss of consciousness (a "blackout"), a body convulsion, unusual movements, or staring spells. Sometimes a contributing factor is a lack of sleep or a high fever. An EEG (electro-encephalogram— recording of the electric currents developed in the brain by means of electrodes applied to the scalp) can help confirm the seizure's presence.

In most cases, seizures can be controlled by a number of medicines called "anticonvulsants." The dosage of the medication is adjusted carefully so that the least possible amount of medication

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will be used to be effective.

Fragile X syndrome. This disorder is the most common inherited form of mental retardation. It was so named because one part of the X chromosome has a defective piece that appears pinched and fragile when under a microscope. Fragile X syndrome affects about two to five percent of people with ASD. It is important to have a child with ASD checked for Fragile X, especially if the parents are considering having another child. For an unknown reason, if a child with ASD also has Fragile X, there is a one-in-two chance that boys born to the same parents will have the syndrome.[5] Other members of the family who may be contemplating having a child may also wish to be checked for the syndrome.

Tuberous Sclerosis. Tuberous sclerosis is a rare genetic disorder that causes benign tumors to grow in the brain as well as in other vital organs. It has a consistently strong association with ASD. One to 4 percent of people with ASD also have tuberous sclerosis.[6]

The Diagnosis of Autism Spectrum Disorders

Although there are many concerns about labeling a young child with an ASD, the earlier the diagnosis of ASD is made, the earlier needed interventions can begin. Evidence over the last 15 years indicates that intensive early intervention in *optimal educational settings for at least 2 years during the preschool years* results in improved outcomes in most young children with ASD.[2]

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In evaluating a child, clinicians rely on behavioral characteristics to make a diagnosis. Some of the characteristic behaviors of ASD may be apparent in the first few months of a child's life, or they may appear at any time during the early years. For the diagnosis, problems in at least one of the areas of communication, socialization, or restricted behavior must be present before the age of 3. The diagnosis requires a two-stage process. The first stage involves developmental screening during 'well child" check-ups; the second stage entails a comprehensive evaluation by a multidisciplinary team.[7]

Screening

A "well child" check-up should include a developmental screening test. If your child's pediatrician does not routinely check your child with such a test, ask that it be done. Your own observations and concerns about your child's development will be essential in helping to screen your child.[7] Reviewing family videotapes, photos, and baby albums can help parents remember when each behavior was first noticed and when the child reached certain developmental milestones.

Several screening instruments have been developed to quickly gather information about a child's social and communicative development within medical settings. Among them are the Checklist of Autism in Toddlers (CHAT),[8] the modified Checklist for Autism in Toddlers (M-CHAT),[9] the Screening Tool for Autism in Two-Year-Olds (STAT),[10] and the Social Communication Questionnaire (SCQ)[11] (for children 4 years of age and older).

Some screening instruments rely solely on parent responses to a questionnaire, and some rely on a combination of parent report and observation. Key items on these instruments that appear to

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differentiate children with autism from other groups before the age of 2 include pointing and pretend play. Screening instruments do not provide individual diagnosis but serve to assess the need for referral for possible diagnosis of ASD. These screening methods may not identify children with mild ASD, such as those with high-functioning autism or Asperger syndrome.

During the last few years, screening instruments have been devised to screen for Asperger syndrome and higher functioning autism. The Autism Spectrum Screening Questionnaire (ASSQ),[12] the Australian Scale for Asperger's Syndrome,[13] and the most recent, the Childhood Asperger Syndrome Test (CAST),[14] are some of the instruments that are reliable for identification of school-age children with Asperger syndrome or higher functioning autism. These tools concentrate on social and behavioral impairments in children without significant language delay.

If, following the screening process or during a routine "well child" check-up, your child's doctor sees any of the possible indicators of ASD, further evaluation is indicated.

Comprehensive Diagnostic Evaluation

The second stage of diagnosis must be comprehensive in order to accurately rule in or rule out an ASD or other developmental problem. This evaluation may be done by a multidisciplinary team that includes a psychologist, a neurologist, a psychiatrist, a speech therapist, or other professionals who diagnose children with ASD.

Because ASD's are complex disorders and may involve other neurological or genetic problems, a comprehensive evaluation should entail neurologic and genetic assessment, along with in-depth cognitive and language testing.[7] In addition, measures developed specifically for diagnosing autism are often used. These

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include the Autism Diagnosis Interview-Revised (ADI-R)[15] and the Autism Diagnostic Observation Schedule (ADOS-G).[16] The ADI-R is a structured interview that contains over 100 items and is conducted with a caregiver. It consists of four main factors—the child's communication, social interaction, repetitive behaviors, and age-of-onset symptoms. The ADOS-G is an observational measure used to "press" for socio-communicative behaviors that are often delayed, abnormal, or absent in children with ASD.

Still another instrument often used by professionals is the Childhood Autism Rating Scale (CARS).[17] It aids in evaluating the child's body movements, adaptation to change, listening response, verbal communication, and relationship to people. It is suitable for use with children over 2 years of age. The examiner observes the child and also obtains relevant information from the parents. The child's behavior is rated on a scale based on deviation from the typical behavior of children of the same age.

Two other tests that should be used to assess any child with a developmental delay are a formal audiologic hearing evaluation and a lead screening. Although some hearing loss can co-occur with ASD, some children with ASD may be incorrectly thought to have such a loss. In addition, if the child has suffered from an ear infection, transient hearing loss can occur. Lead screening is essential for children who remain for a long period of time in the oral-motor stage in which they put any and everything into their mouths. Children with an autistic disorder usually have elevated blood lead levels.[7]

Customarily, an expert diagnostic team has the responsibility of thoroughly evaluating the child, assessing the child's unique strengths and weaknesses, and determining a formal diagnosis.

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The team will then meet with the parents to explain the results of the evaluation.

Although parents may have been aware that something was not "quite right" with their child, when the diagnosis is given, it is a devastating blow. At such a time, it is hard to stay focused on asking questions. But while members of the evaluation team are together is the best opportunity the parents will have to ask questions and get recommendations on what further steps they should take for their child. Learning as much as possible at this meeting is very important, but it is helpful to leave this meeting with the name or names of professionals who can be contacted if the parents have further questions.

Available Aids

When your child has been evaluated and diagnosed with an autism spectrum disorder, you may feel inadequate to help your child develop to the fullest extent of his or her ability. As you begin to look at treatment options and at the types of aid available for a child with a disability, you will find out that there is help for you. It is going to be difficult to learn and remember everything you need to know about the resources that will be most helpful. *Write down everything.* If you keep a notebook, you will have a foolproof method of recalling information. Keep a record of the doctors' reports and the evaluation your child has been given so that his or her eligibility for special programs will be documented. Learn everything you can about special programs for your child; the more you know, the more effectively you can advocate.

For every child eligible for special programs, each state guarantees special education and related services. The Individuals

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with Disabilities Education Act (IDEA) is a Federally mandated program that assures a free and appropriate public education for children with diagnosed learning deficits. Usually children are placed in public schools and the school district pays for all necessary services. These will include, as needed, services by a speech therapist, occupational therapist, school psychologist, social worker, school nurse, or aide.

By law, the public schools must prepare and carry out a set of instruction goals, or specific skills, for every child in a special education program. The list of skills is known as the child's Individualized Education Program (IEP). The IEP is an agreement between the school and the family on the child's goals. When your child's IEP is developed, you will be asked to attend the meeting. There will be several people at this meeting, including a special education teacher, a representative of the public schools who is knowledgeable about the program, other individuals invited by the school or by you (you may want to bring a relative, a child care provider, or a supportive close friend who knows your child well). Parents play an important part in creating the program, as they know their child and his or her needs best. Once your child's IEP is developed, a meeting is scheduled once a year to review your child's progress and to make any alterations to reflect his or her changing needs.

If your child is under 3 years of age and has special needs, he or she should be eligible for an early intervention program; this program is available in every state. Each state decides which agency will be the lead agency in the early intervention program. The early intervention services are provided by workers qualified to care for toddlers with disabilities and are usually in the child's home

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or a place familiar to the child. The services provided are written into an Individualized Family Service Plan (IFSP) that is reviewed at least once every 6 months. The plan will describe services that will be provided to the child, but will also describe services for parents to help them in daily activities with their child and for siblings to help them adjust to having a brother or sister with ASD.

There is a list of resources at the back of the brochure that will be helpful to you as you look for programs for your child.

Treatment Options

There is no single best treatment package for all children with ASD. One point that most professionals agree on is that early intervention is important; another is that most individuals with ASD respond well to highly structured, specialized programs.

Before you make decisions on your child's treatment, you will want to gather information about the various options available. Learn as much as you can, look at all the options, and make your decision on your child's treatment based on your child's needs. You may want to visit public schools in your area to see the type of program they offer to special needs children.

Guidelines used by the Autism Society of America include the following questions parents can ask about potential treatments:

- Will the treatment result in harm to my child?
- How will failure of the treatment affect my child and family?
- Has the treatment been validated scientifically?
- Are there assessment procedures specified?
- How will the treatment be integrated into my child's current program? Do not become so infatuated with a given

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treatment that functional curriculum, vocational life and social skills are ignored.

The National Institute of Mental Health suggests a list of questions parents can ask when planning for their child:

- How successful has the program been for other children?
- How many children have gone on to placement in a regular school and how have they performed?
- Do staff members have training and experience in working with children and adolescents with autism?
- How are activities planned and organized?
- Are there predictable daily schedules and routines?
- How much individual attention will my child receive?
- How is progress measured? Will my child's behavior be closely observed and recorded?
- Will my child be given tasks and rewards that are personally motivating?
- Is the environment designed to minimize distractions?
- Will the program prepare me to continue the therapy at home?
- What is the cost, time commitment, and location of the program?

Among the many methods available for treatment and education of people with autism, applied behavior analysis (ABA) has become widely accepted as an effective treatment. *Mental Health: A Report of the Surgeon General* states, "Thirty years of research demonstrated the efficacy of applied behavioral methods in reducing inappropriate behavior and in increasing communication, learning, and appropriate social behavior."[18] The basic research

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done by Ivar Lovaas and his colleagues at the University of California, Los Angeles, calling for an intensive, one-on-one child-teacher interaction for 40 hours a week, laid a foundation for other educators and researchers in the search for further effective early interventions to help those with ASD attain their potential. The goal of behavioral management is to reinforce desirable behaviors and reduce undesirable ones.[19,20]

An effective treatment program will build on the child's interests, offer a predictable schedule, teach tasks as a series of simple steps, actively engage the child's attention in highly structured activities, and provide regular reinforcement of behavior. Parental involvement has emerged as a major factor in treatment success. Parents work with teachers and therapists to identify the behaviors to be changed and the skills to be taught. Recognizing that parents are the child's earliest teachers, more programs are beginning to train parents to continue the therapy at home.

As soon as a child's disability has been identified, instruction should begin. Effective programs will teach early communication and social interaction skills. In children younger than 3 years, appropriate interventions usually take place in the home or a child care center. These interventions target specific deficits in learning, language, imitation, attention, motivation, compliance, and initiative of interaction. Included are behavioral methods, communication, occupational and physical therapy along with social play interventions. Often the day will begin with a physical activity to help develop coordination and body awareness; children string beads, piece puzzles together, paint, and participate in other motor skills activities. At snack time the teacher encourages social interaction and models how to use language to ask for more juice. The children learn by doing. Working with the children are

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students, behavioral therapists, and parents who have received extensive training. In teaching the children, positive reinforcement is used.[21]

Children older than 3 years usually have school-based, individualized, special education. The child may be in a segregated class with other autistic children or in an integrated class with children without disabilities for at least part of the day. Different localities may use differing methods but all should provide a structure that will help the children learn social skills and, functional communication. In these programs, teachers often involve the parents, giving useful advice in how to help their child use the skills or behaviors learned at school when they are at home.[22]

In elementary school, the child should receive help in any skill area that is delayed and, at the same time, be encouraged to grow in his or her areas of strength. Ideally, the curriculum should be adapted to the individual child's needs. Many schools today have an inclusion program in which the child is in a regular classroom for most of the day, with special instruction for a part of the day. This instruction should include such skills as learning how to act in social situations and in making friends. Although higher-functioning children may be able to handle academic work, they too need help to organize tasks and avoid distractions.

During middle and high school years, instruction will begin to address such practical matters as work, community living, and recreational activities. This should include work experience, using public transportation, and learning skills that will be important in community living.[23]

All through your child's school years, you will want to be an active participant in his or her education program. Collaboration

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The Adolescent Years

Adolescence is a time of stress and confusion; and it is no less so for teenagers with autism. Like all children, they need help in dealing with their budding sexuality. While some behaviors improve during the teenage years, some get worse. Increased autistic or aggressive behavior may be one way some teens express their newfound tension and confusion.

The teenage years are also a time when children become more socially sensitive. At the age that most teenagers are concerned with acne, popularity, grades, and dates, teens with autism may become painfully aware that they are different from their peers. They may notice that they lack friends. And unlike their schoolmates, they aren't dating or planning for a career. For some, the sadness that comes with such realization motivates them to learn new behaviors and acquire better social skills.

between parents and educators is essential in evaluating your child's progress.

Dietary and Other Interventions

In an effort to do everything possible to help their children, many parents continually seek new treatments. Some treatments are developed by reputable therapists or by parents of a child with ASD. Although an unproven treatment may help one child, it may not prove beneficial to another. To be accepted as a proven treatment, the treatment should undergo clinical trials, preferably randomized, double-blind trials, that would allow for a comparison between treatment and no treatment. Following are some of the interventions that have been reported to have been helpful to some children but whose efficacy or safety has not been proven.

Dietary interventions are based on the idea that 1) food allergies cause symptoms of autism, and 2) an insufficiency of a specific vitamin or mineral may cause some autistic symptoms. If

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parents decide to try for a given period of time a special diet, they should be sure that the child's nutritional status is measured carefully.

A diet that some parents have found was helpful to their autistic child is a gluten-free, casein-free diet. Gluten is a casein-like substance that is found in the seeds of various cereal plants—wheat, oat, rye, and barley. Casein is the principal protein in milk. Since gluten and milk are found in many of the foods we eat, following a gluten-free, casein-free diet is difficult.

A supplement that some parents feel is beneficial for an autistic child is Vitamin B6, taken with magnesium (which makes the vitamin effective). The result of research studies is mixed; some children respond positively, some negatively, some not at all or very little.[4]

In the search for treatment for autism, there has been discussion in the last few years about the use of secretin, a substance approved by the Food and Drug Administration (FDA) for a single dose normally given to aid in diagnosis of a gastrointestinal problem. Anecdotal reports have shown improvement in autism symptoms, including sleep patterns, eye contact, language skills, and alertness. Several clinical trials conducted in the last few years have found no significant improvements in symptoms between patients who received secretin and those who received a placebo.[24]

Medications Used in Treatment

Medications are often used to treat behavioral problems, such as aggression, self-injurious behavior, and severe tantrums, that keep the person with ASD from functioning more effectively at home or school. The medications used are those that have been developed to treat similar symptoms in other disorders. Many of these

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medications are prescribed "off-label." This means they have not been officially approved by the FDA for use in children, but the doctor prescribes the medications if he or she feels they are appropriate for your child. Further research needs to be done to ensure not only the efficacy but the safety of psychotropic agents used in the treatment of children and adolescents.

A child with ASD may not respond in the same way to medications as typically developing children. It is important that parents work with a doctor who has experience with children with autism. A child should be monitored closely while taking a medication. The doctor will prescribe the lowest dose possible to be effective. Ask the doctor about any side effects the medication may have and keep a record of how your child responds to the medication. It will be helpful to read the "patient insert" that comes with your child's medication. Some people keep the patient inserts in a small notebook to be used as a reference. This is most useful when several medications are prescribed.

Anxiety and depression. The selective serotonin reuptake inhibitors (SSRI's) are the medications most often prescribed for symptoms of anxiety, depression, and/or obsessive-compulsive disorder (OCD). Only one of the SSRI's, fluoxetine, (Prozac®) has been approved by the FDA for both OCD and depression in children age 7 and older. Three that have been approved for OCD are fluvoxamine (Luvox®), age 8 and older; sertraline (Zoloft®), age 6 and older; and clomipramine (Anafranil®), age 10 and older.[4] Treatment with these medications can be associated with decreased frequency of repetitive, ritualistic behavior and improvements in eye contact and social contacts. The FDA is studying and analyzing

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data to better understand how to use the SSRI's safely, effectively, and at the lowest dose possible.

Behavioral problems. Antipsychotic medications have been used to treat severe behavioral problems. These medications work by reducing the activity in the brain of the neurotransmitter dopamine. Among the older, typical antipsychotics, such as haloperidol (Haldol®), thioridazine, fluphenazine, and chlorpromazine, haloperidol was found in more than one study to be more effective than a placebo in treating serious behavioral problems.[25] However, haloperidol, while helpful for reducing symptoms of aggression, can also have adverse side effects, such as sedation, muscle stiffness, and abnormal movements.

Placebo-controlled studies of the newer "atypical" antipsychotics are being conducted on children with autism. The first such study, conducted by the NIMH-supported Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, was on risperidone (Risperdal®).[26] Results of the 8-week study were reported in 2002 and showed that risperidone was effective and well tolerated for the treatment of severe behavioral problems in children with autism. The most common side effects were increased appetite, weight gain and sedation. Further long-term studies are needed to determine any long-term side effects. Other atypical antipsychotics that have been studied recently with encouraging results are olanzapine (Zyprexa®) and ziprasidone (Geodon®). Ziprasidone has not been associated with significant weight gain.

Seizures. Seizures are found in one in four persons with ASD, most often in those who have low IQ or are mute. They are treated with one or more of the anticonvulsants. These include such medications as carbamazepine (Tegretol®), lamotrigine (Lamictal®), topiramate (Topamax®), and valproic acid (Depakote®). The level

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of the medication in the blood should be monitored carefully and adjusted so that the least amount possible is used to be effective. Although medication usually reduces the number of seizures, it cannot always eliminate them.

Inattention and hyperactivity. Stimulant medications such as methylphenidate (Ritalin®), used safely and effectively in persons with attention deficit hyperactivity disorder, have also been prescribed for children with autism. These medications may decrease impulsivity and hyperactivity in some children, especially those higher functioning children.

Several other medications have been used to treat ASD symptoms; among them are other antidepressants, naltrexone, lithium, and some of the benzodiazepines such as diazepam (Valium®) and lorazepam (Ativan®). The safety and efficacy of these medications in children with autism has not been proven. Since people may respond differently to different medications, your child's unique history and behavior will help your doctor decide which medication might be most beneficial.

Adults with an Autism Spectrum Disorder

Some adults with ASD, especially those with high-functioning autism or with Asperger syndrome, are able to work successfully in mainstream jobs. Nevertheless, communication and social problems often cause difficulties in many areas of life. They will continue to need encouragement and moral support in their struggle for an independent life.

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Many others with ASD are capable of employment in sheltered workshops under the supervision of managers trained in working with persons with disabilities. A nurturing environment at home, at school, and later in job training and at work, helps persons with ASD continue to learn and to develop throughout their lives.

The public schools' responsibility for providing services ends when the person with ASD reaches the age of 22. The family is then faced with the challenge of finding living arrangements and employment to match the particular needs of their adult child, as well as the programs and facilities that can provide support services to achieve these goals. Long before your child finishes school, you will want to search for the best programs and facilities for your young adult. If you know other parents of ASD adults, ask them about the services available in your community. If your community has little to offer, serve as an advocate for your child and work toward the goal of improved employment services. Research the resources listed in the back of this brochure to learn as much as possible about the help your child is eligible to receive as an adult.

Living Arrangements for the Adult with an Autism Spectrum Disorder

Independent living. Some adults with ASD are able to live entirely on their own. Others can live semi-independently in their own home or apartment if they have assistance with solving major problems, such as personal finances or dealing with the government agencies that provide services to persons with disabilities. This assistance can be provided by family, a professional agency, or another type of provider.

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Living at home. Government funds are available for families that choose to have their adult child with ASD live at home. These programs include Supplemental Security Income (SSI), Social Security Disability Insurance (SSDI), Medicaid waivers, and others. Information about these programs is available from the Social Security Administration (SSA). An appointment with a local SSA office is a good first step to take in understanding the programs for which the young adult is eligible.

Foster homes and skill-development homes. Some families open their homes to provide long-term care to unrelated adults with disabilities. If the home teaches self-care and housekeeping skills and arranges leisure activities, it is called a "skill-development" home.

Supervised group living. Persons with disabilities frequently live in group homes or apartments staffed by professionals who help the individuals with basic needs. These often include meal preparation, housekeeping, and personal care needs. Higher functioning persons may be able to live in a home or apartment where staff only visit a few times a week. These persons generally prepare their own meals, go to work, and conduct other daily activities on their own.

Institutions. Although the trend in recent decades has been to avoid placing persons with disabilities into long-term-care institutions, this alternative is still available for persons with ASD who need intensive, constant supervision. Unlike many of the institutions years ago, today's facilities view residents as individuals with human needs and offer opportunities for recreation and simple but meaningful work.

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Research into Causes and Treatment of Autism Spectrum Disorders

Research into the causes, the diagnosis, and the treatment of autism spectrum disorders has advanced in tandem. With new well-researched standardized diagnostic tools, ASD can be diagnosed at an early age. And with early diagnosis, the treatments found to be beneficial in recent years can be used to help the child with ASD develop to his or her greatest potential.

In the past few years, there has been public interest in a theory that suggested a link between the use of thimerosal, a mercury-based preservative used in the measles-mumps-rubella (MMR) vaccine, and autism. Although mercury is no longer found in childhood vaccines in the United States, some parents still have concerns about vaccinations. Many well-done, large-scale studies have now been done that have failed to show a link between thimerosal and autism. A panel from the Institute of Medicine is now examining these studies, including a large Danish study that concluded that there was no causal relationship between childhood vaccination using thimerosal-containing vaccines and the development of an autism spectrum disorder,[27] and a U.S. study looking at exposure to mercury, lead, and other heavy metals.

Research on the Biologic Basis of ASD

Because of its relative inaccessibility, scientists have only recently been able to study the brain systematically. But with the emergence of new brain imaging tools—computerized tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging

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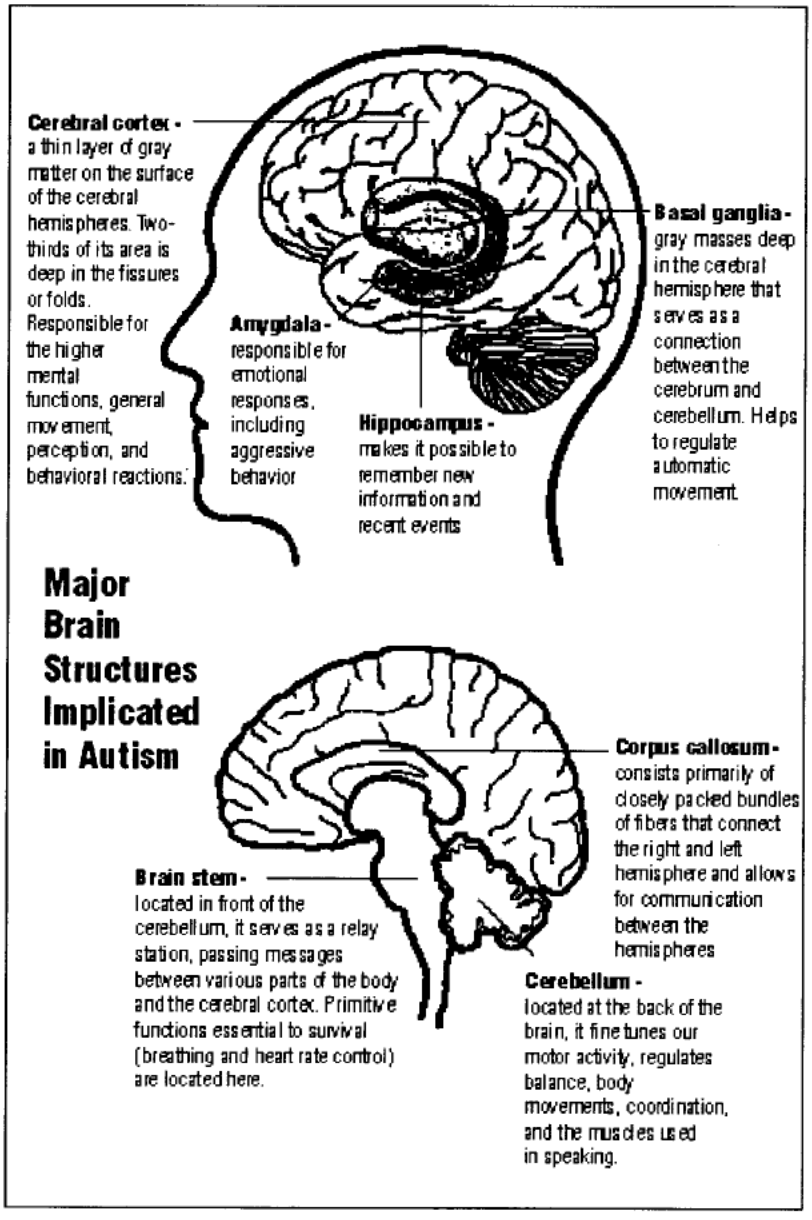

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(MRI), study of the structure and the functioning of the brain can be done. With the aid of modern technology and the new availability of both normal and autism tissue samples to do postmortem studies, researchers will be able to learn much through comparative studies.

Postmortem and MRI studies have shown that many major brain structures are implicated in autism. This includes the cerebellum, cerebral cortex, limbic system, corpus callosum, basal ganglia, and brain stem.[28] Other research is focusing on the role of neurotransmitters such as serotonin, dopamine, and epinephrine.

Research into the causes of autism spectrum disorders is being fueled by other recent developments. Evidence points to genetic factors playing a prominent role in the causes for ASD. Twin and family studies have suggested an underlying genetic vulnerability to ASD.[29] To further research in this field, the Autism Genetic Resource Exchange, a project initiated by the Cure Autism Now Foundation, and aided by an NIMH grant, is recruiting genetic samples from several hundred families. Each family with more than one member diagnosed with ASD is given a 2-hour, in-home screening. With a large number of DNA samples, it is hoped that the most important genes will be found. This will enable scientists to learn what the culprit genes do and how they can go wrong.

Another exciting development is the Autism Tissue Program (http://www.brainbank.org), supported by the Autism Society of America Foundation, the Medical Investigation of Neuro-developmental Disorders (M.I.N.D.) Institute at the University of California, Davis, and the National Alliance for Autism Research. The program is aided by a grant to the Harvard Brain and Tissue Resource Center (http://www.brainbank.mclean.org), funded by the National Institute of Mental Health (NIMH) and the National

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Institute of Neurological Disorders and Stroke (NINDS). Studies of the postmortem brain with imaging methods will help us learn why some brains are large, how the limbic system develops, and how the brain changes as it ages. Tissue samples can be stained and will show which neurotransmitters are being made in the cells and how they are transported and released to other cells. By focusing on specific brain regions and neurotransmitters, it will become easier to identify susceptibility genes.

Recent neuroimaging studies have shown that a contributing cause for autism may be abnormal brain development beginning in the infant's first months. This "growth dysregulation hypothesis" holds that the anatomical abnormalities seen in autism are caused by genetic defects in brain growth factors. It is possible that sudden, rapid head growth in an infant may be an early warning signal that will lead to early diagnosis and effective biological intervention or possible prevention of autism.[30]

For detailed information on autism spectrum disorders research, see NIMH research fact sheet, *Autism Spectrum Disorders Research* at http://www.nimh.nih.gov/publicat/autismresfact.cfm.

The Children's Health Act of 2000—What It Means to Autism Research

The Children's Health Act of 2000 was responsible for the creation of the Interagency Autism Coordinating Committee (IACC), a committee that includes the directors of five NIH institutes—the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Child Health and Human Development (NICHD), and the National Institute

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of Environmental Health Sciences (NIEHS)—as well as representatives from the Health Resource Services Administration, the National Center on Birth Defects and Developmental Disabilities (a part of the Centers for Disease Control), the Agency for Toxic Substances and Disease Registry, the Substance Abuse and Mental Health Services Administration, the Administration on Developmental Disabilities, the Centers for Medicare and Medicaid Services, the U.S. Food and Drug Administration, and the U.S. Department of Education. The Committee, instructed by the Congress to develop a 10-year agenda for autism research, introduced the plan, dubbed a "matrix" or a "roadmap," at the first Autism Summit Conference in November 2003. The roadmap indicates priorities for research for years 1 to 3, years 4 to 6, and years 7 to 10.

The five NIH institutes of the IACC have established the Studies to Advance Autism Research and Treatment (STAART) Network, composed of eight network centers. They will conduct research in the fields of developmental neurobiology, genetics, and psychopharmacology. Each center is pursuing its own particular mix of studies, but there also will be multi-site clinical trials within the STAART network.

The STAART centers are located at the following sites:

- University of North Carolina, Chapel Hill
- Yale University, Connecticut
- University of Washington, Seattle
- University of California, Los Angeles
- Mount Sinai Medical School, New York
- Kennedy Krieger Institute, Maryland
- Boston University, Massachusetts
- University of Rochester, New York

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A data coordination center will analyze the data generated by both the STAART network and the Collaborative Programs of Excellence in Autism (CPEA). This latter program, funded by the NICHD and the NIDCD Network on the Neurobiology and Genetics of Autism, consists of 10 sites. The CPEA is at present studying the world's largest group of well-diagnosed individuals with autism characterized by genetic and developmental profiles.

The CPEA centers are located at:

- Boston University, Massachusetts
- University of California, Davis
- University of California, Irvine
- University of California, Los Angeles
- Yale University, Connecticut
- University of Washington, Seattle
- University of Rochester, New York
- University of Texas, Houston
- University of Pittsburgh, Pennsylvania
- University of Utah, Salt Lake City

The NIEHS has programs (http://www.niehs.nih.gov/translat/children/ctr-desc.htm) at:

- Center for Childhood Neurotoxicology and Assessment, University of Medicine & Dentistry, New Jersey
- The Center for the Study of Environmental Factors in the Etiology of Autism, University of California, Davis

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Addendum to Autism Spectrum Disorders

January 2007

This addendum to the booklet *Autism Spectrum Disorders* was prepared to clarify information contained in the booklet; and to provide updated information on the prevalence of autism spectrum disorders. This addendum also applies to the Autism Spectrum Disorders Web page document.

Prevalence

In 2003 - the most recent government study on the rate of autism - the Centers for Disease Control (CDC) found that the rate is higher than the rates found from studies conducted in the United States during the 1980s and early 1990s. This study was consistent with the rate found in other more recent studies. Debate continues about whether this represents a true increase in prevalence. Changes in the criteria used to diagnose autism, along with increased recognition of the disorder by professionals and the public may all be contributing factors. Nonetheless, it is clear that more children are being diagnosed with an ASD than ever before.

Data from the CDC's Atlanta-based program found the rate of autism spectrum disorder was 3.4 per 1,000 for children 3 to 10 years of age. Summarizing this and several other major studies on autism prevalence, CDC estimates that 2–6 per 1,000 (from 1 in 500 to 1 in 166) children have an ASD. Compared to the prevalence of other childhood conditions, this rate is lower than the rate of mental retardation (9.7 per 1,000 children), but higher than the rates for cerebral palsy (2.8 per 1,000 children), hearing loss (1.1 per 1,000 children), and vision impairment (0.9 per 1,000 children).[1] For additional data, please visit the CDC Web site.

Fragile X

The original booklet and Web page contains the following statement about inheriting Fragile X Syndrome:

> "For an unknown reason, if a child with ASD also has Fragile X, there is a one-in-two chance that boys born to the same parents will have the syndrome.[2] Other members of the family who may be contemplating having a child may also wish to be checked for the syndrome."

A distinction can be made between a father's and mother's ability to pass along to a daughter or son the altered gene on the X chromosome that is linked to fragile X syndrome. Because both males (XY) and females (XX) have at least one X chromosome, both can pass on the mutated gene to their children.

A father with the altered gene for Fragile X on his X chromosome will only pass that gene on to his daughters. He passes a Y chromosome on to his sons, which doesn't transmit the condition. Therefore, if the father has the altered gene on his X chromosome, but the mother's X

---

[1] Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of Autism in a US Metropolitan Area. *The Journal of the American Medical Association.*. 2003 Jan 1;289(1):49-55.

[2] Powers MD. What Is Autism? In: Powers MD, ed. *Children with Autism: A Parent's Guide, Second Edition.* Bethesda, MD: Woodbine House, 2000, 28.

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chromosomes are normal, all of the couple's daughters would have the altered gene for Fragile X, while none of their sons would have the mutated gene.

Because mothers pass on only X chromosomes to their children, if the mother has the altered gene for Fragile X, she can pass that gene to either her sons or her daughters. If the mother has the mutated gene on one X chromosome and has one normal X chromosome, and the father has no genetic mutations, all the children have a 50-50 chance of inheriting the mutated gene.

The odds noted here apply to each child the parents have.[3]
In terms of prevalence, the latest statistics are consistent in showing that 5% of people with autism are affected by fragile X and 10% to 15% of those with fragile X show autistic traits.

Medications

On October 6, 2006 the U.S. Food and Drug Administration (FDA) approved risperidone (generic name) or Risperdal (brand name) for the symptomatic treatment of irritability in autistic children and adolescents ages 5 to 16. The approval is the first for the use of a drug to treat behaviors associated with autism in children. These behaviors are included under the general heading of irritability, and include aggression, deliberate self-injury and temper tantrums.

Olanzapine (Zyprexa) and other antipsychotic medications are used "off-label" for the treatment of aggression and other serious behavioral disturbances in children, including children with autism. Off-label means a doctor will prescribe a medication to treat a disorder or in an age group that is not included among those approved by the FDA.

Other medications are used to address symptoms or other disorders in children with autism. Fluoxetine (Prozac) and sertraline (Zoloft) are approved by the FDA for children age 7 and older with obsessive-compulsive disorder. Fluoxetine is also approved for children age 8 and older for the treatment of depression.

Fluoxetine and sertraline are antidepressants known as selective serotonin reuptake inhibitors (SSRIs). Despite the relative safety and popularity of SSRIs and other antidepressants, some studies have suggested that they may have unintentional effects on some people, especially adolescents and young adults. In 2004, after a thorough review of data, the Food and Drug Administration (FDA) adopted a "black box" warning label on all antidepressant medications to alert the public about the potential increased risk of suicidal thinking or attempts in children and adolescents taking antidepressants. In 2007, the agency extended the warning to include young adults up to age 25. A "black box" warning is the most serious type of warning on prescription drug labeling. The warning emphasizes that children, adolescents and young adults taking antidepressants should be closely monitored, especially during the initial weeks of treatment, for any worsening depression, suicidal thinking or behavior, or any unusual changes in behavior such as sleeplessness, agitation, or withdrawal from normal social situations.

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[3] *Families and Fragile X Syndrome*: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Child Health and Human Development. 2003

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Disorders/Vaccinations

The Institute of Medicine (IOM) conducted a thorough review on the issue of a link between thimerosal (a mercury based preservative that is no longer used in vaccinations) and autism. The final report from IOM, Immunization Safety Review: Vaccines and Autism, released in May 2004, stated that the committee did not find a link.

Until 1999, vaccines given to infants to protect them against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and Hepatitis B contained thimerosal as a preservative. Today, with the exception of some flu vaccines, none of the vaccines used in the U.S. to protect preschool aged children against 12 infectious diseases contain thimerosal as a preservative. The MMR vaccine does not and never did contain thimerosal. Varicella (chickenpox), inactivated polio (IPV), and pneumococcal conjugate vaccines have also never contained thimerosal.

A U.S. study looking at environmental factors including exposure to mercury, lead and other heavy metals is ongoing.

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For Further Information

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E-mail: nimhinfo@nih.gov
Web site: http://www.nimh.nih.gov

For additional information visit the NIMH web site at http://www.nimh.nih.gov

For further information on autism spectrum disorders, go to MedlinePlus®, a service of the U.S. National Library of Medicine and the National Institutes of Health at the following web site: http://www.nlm.nih.gov/medlineplus/autism.html

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This brochure was written by Margaret Strock, Office of Communications, NIMH. Scientific information and review were provided by NIMH staff members Thomas Insel, MD; Stephen Foote, MD; Ann Wagner, PhD; Audrey Thurm, PhD; Benjamin Vitiello, MD; Douglas Meinecke, PhD; and Judith Cooper, PhD, National Institute on Deafness and Other Communication Disorders. Editorial assistance and graphic assistance was provided by Ruth Dubois, Antoinette Cooper, and Catherine West.

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT update for Neuroimaging
Date: Monday, June 22, 2009 2:46:19 PM
Attachments: SUPPORTNeuroUpdateJune2009.doc

--

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SUPPORT Neuroimaging secondary update — Susan Hintz
NRN Steering Committee meeting June 2009

Enrollment/Process/Follow-up update

- 16 sites have participated in SUPPORT Neuroimaging secondary
  - 661 patients were enrolled in the SUPPORT Neuroimaging secondary
    - **533 patients** have completed neuroimaging including successful 35-42 week MRI (as of 5/31/09 monthly report)
      - Of 127 patients enrolled who do not have MRI:
        - 87 patients died before MRI
        - 10 with MRI01 not yet complete
        - 30 with other issues including technical/availability (4), attempted but movement or uncooperative (5), patient discharged or transferred prior to MRI, or missed (7), clinically unstable (6), withdrew consent (4), other (4)
  - 18-22 month follow-up so far -
    - **196 patients** in this cohort with near-term MRI's who survived to discharge will have 18-22 month follow-up windows **closed** as of 7/1/09
      - **177 have completed 18-22 month visit**
        - 5 formally reported lost to follow-up;
        - 2 are reported going to be followed at another center;
        - 7 have not been seen yet
        - 5 died after discharge
          - **177/191 = ~93% follow-up rate among survivors**

Neuroimaging

- Many thanks to the site coordinators for their enormous efforts in enrolling, following through with all neuroimaging, and providing readable imaging!
- CUS central reading –
  - First 2-day central reading May 9 & 10; ~40% of CUS completed
  - Second (and hopefully final) 2-day CUS central reading August 23 & 24
- MRI central reading
  - Dr. Barnes currently reading; also, central reading Stanford on June 29th
  - 2nd reader for random sample of the MRI's to establish reliability
    - White matter injury summary classifications (based on previously published criteria from Miller, Inder) with previously reported reliability data
    - Preliminary calculations (Abhik Das) suggests ~80-100 MRI's would need to be read.
- **THANK YOU to RTI and NICHD (especially Meg, Kris, Carolyn, Jamie, and Rose!) for their enormous help with this huge job!**

SUPPORT Neuroimaging: Extended Follow-Up

- Separate update later this afternoon

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From: Gantz, Marie
To: Wilson, Leslie Dawn; Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline
Subject: RE: SUPPORT
Date: Monday, June 22, 2009 11:37:26 AM

Hi Leslie,

To answer your question about infant (b) (6) , the infant currently has SUPP10 question "Final ROP status determined at 18M Follow Up?" answered as No. However, the infant has not yet reached 18 months adjusted age. Unless you are sure that there is no chance of obtaining ROP status at FU, this question should be left blank until the infant is old enough to have the FU visit. Leaving the question blank will prompt us to send you a reminder to obtain ROP information when the FU window opens. If the question is answered No prematurely then you will not receive that reminder. If for some reason you are sure that there is no chance of obtaining ROP status at the FU visit, then you can leave the question answered No but please enter an F5 to explain why the question was answered before the infant reached 18 months adjusted age. Otherwise, please change the answer from No to missing.

Also, regarding infant (b) (6) , not sure what you mean by "a week of his earlier stay is missing. We are waiting to see if it scans in when he is discharged." However, I think you can wait until the infant is discharged to enter the data on the NG07. In the meantime, you will continue to receive reminders until the data are entered.

Thanks, and let me know if you have any other questions.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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(b) (6)

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Monday, June 22, 2009 10:02 AM
To: "Higgins, Rosemary (NIH/NICHD) [E]"; Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline
Cc: Gantz, Marie; Hamer, Faithe Angeline
Subject: RE: SUPPORT

Hi.

See below:

Kind Regards-

Leslie Dawn Wilson, BSN, CCRC
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 17, 2009 2:24 PM
To: Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn; Hamer, Faithe Angeline
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. F/U visit this week
12	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.--I am not quite sure what you are asking for us to do-would you please clarify? Thank you
CENTER	NETWORK	BPD_message
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. This pt is still in the hospital and a week of his earlier stay is missing. We are waiting to see if it scans in when he is discharged. However if you would like for us to just enter "missing data", we will. Please advise.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. This data has been entered
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. This pt is still in the hospital
CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF09a has not been completed. This will be entered this week.
12	(b) (6)	FU window has closed but NF09a has not been completed. This will be entered this week.

Rosemary D. Higgins, MD
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; "Michele Walsh"; "Bradley Yoder"; "Roger Faix"; "Abbot Laptook"; "kurt.schibler@cchmc.org"; "Das, Abhik"; "Nancy Newman"; "Gantz, Marie"; "Poole, W. Kenneth"
Cc: "Petrie, Carolyn"; "Zaterka-Baxter, Kristin"; Rich, Wade; Martinez, Fernando
Subject: RE: SUPPORT Updates
Date: Sunday, June 21, 2009 1:37:42 PM
Attachments: Antenatal Consent Paper 6_15 .doc

Hello Everyone
Congratulations on a job very well done!!
Marie has prepared the following summary for our meeting

SUPPORT Update 6/19/2009

Total enrollment of 1317 was completed in February 2009. The primary outcomes of BPD/death and ROP/death are still unknown for 14 and 140 infants, respectively.

	ROP/death		
BPD/death	**Known**	**Unknown**	**Total**
Known	1172	131	1303
Unknown	5	9	14
Total	1177	140	1317

Infants with known outcomes for BPD/death and ROP/death

The last SUPPORT infant reached 36 weeks PMA in late May, so we should have complete data on the BPD outcome shortly. Historically, by 55 weeks PMA we have known ROP status for 100% of the infants with an adverse outcome and about 92% of the infants with a positive outcome. The last SUPPORT infant will reach 55 weeks PMA at the end of September.

To date, 778 (59%) of SUPPORT infants have a known outcome for NDI/death at 18-22 months adjusted age. The last follow up window will open in December 2010 and will close in April 2011.

She will try to get us some overall oximeter data if possible

I will be starting to develop the manuscript
We are planning a visit to RTI and Wally will join us there at the end of August – hopefully when we can close the neonatal endpoints of ROP/BPD. We should have the BPD data within a few weeks
The plan is to develop 2 manuscripts –
CPAP vs Surfactant
High vs Lower SpO2

I suspect that we will be ready with the first within 2 months
And the second in 3 months
We would obviously submit as soon as they are ready – Probably NEJM

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We need to complete the follow-up and we are well on the way with almost 60% of those outcomes available
The very first manuscript will be the consent manuscript which is now circulating to the authors. I have attached for your comments

Points for discussion:

1. Where should the data be presented??

It will be ready well ahead of PAS.
There will probably be new data for PAS – Secondaries etc

2. Need status reports for all secondaries
3. Continue to get all final infant data, especially ROP data, and complete follow-up
4. Any additional bisuness??

Safe travels
Neil

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled. Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the

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study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to

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the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

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2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the ability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways as shown in Table 1. Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to

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antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance (p=0.0011) and to have received prenatal care (p=0.0039), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, p<0.0001) (Table 2).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers belonged to a second maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

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Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for

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all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[7] However, these controls only protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[8,9] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [10] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [11] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[12] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[13] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[14]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point

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toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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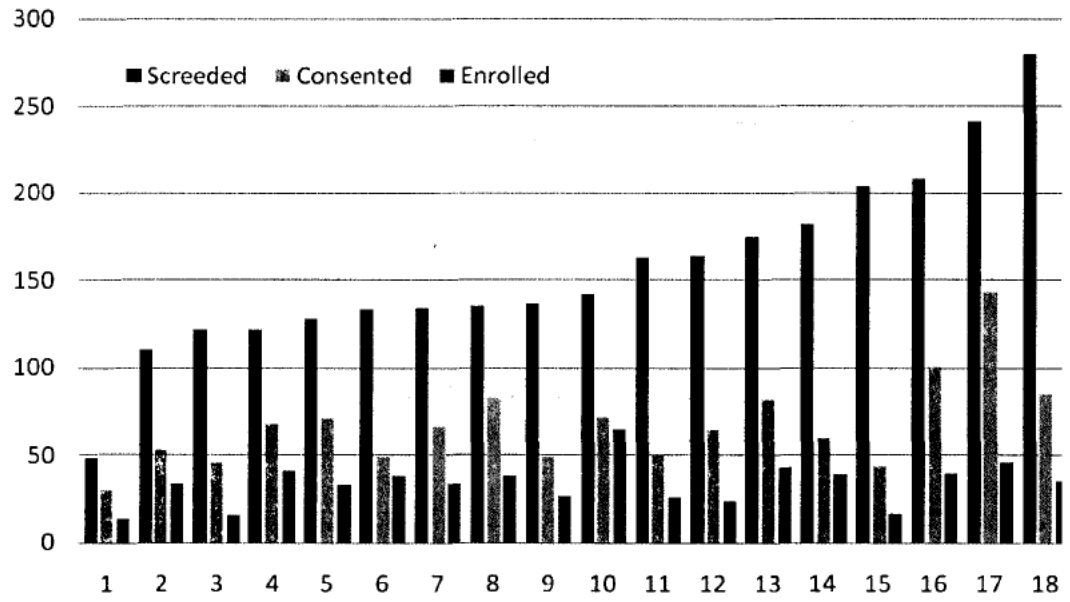

Figure 1. Women who were screened, consented, and enrolled by Center

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 1 Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039

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No Antenatal Steroids	3.8	15.7	<.0001

Table 2. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 2 Reasons for not approaching mothers for consent.

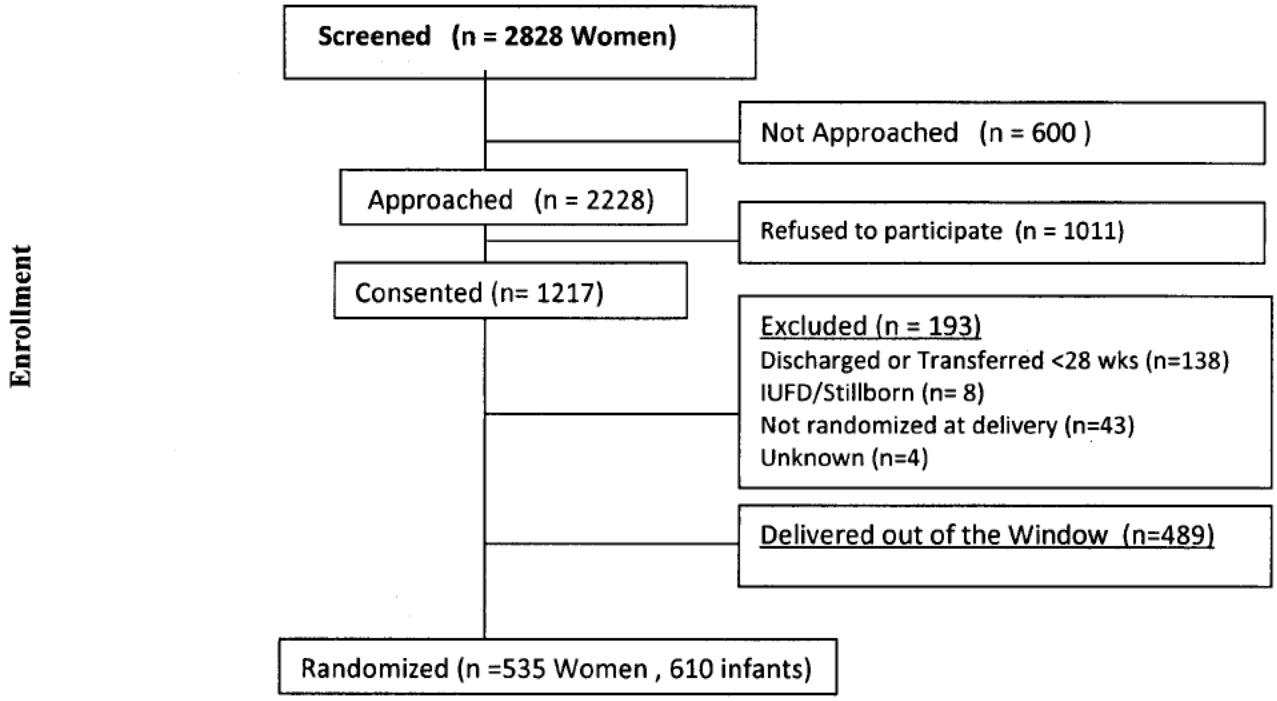

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Gloria Siaw
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu; Ronald GOldberg; Ricki F Goldstein; Kimberley.fisher@duke.edu; Melody B Lohmeyer; Gantz, Marie
Subject: Re: SUPPORT
Date: Thursday, June 18, 2009 5:58:42 PM

Hi Rose,

We have schedule the following patients for their follow-up visit on (b) (6). Thank you reminder.

19 (b) (6)

19 (b) (6)

Sincerely,

Gloria

Gloria Siaw, BSN, BS, CRA
Clinical Research Coordinator
Dept of Pediatrics/Neonatology
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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

06/17/2009 02:10 PM

To "Ronald GOldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Melody B Lohmeyer" <lohme001@mc.duke.edu>, <Kimberley.fisher@duke.edu>, <gloria.siaw@duke.edu>, <cotte010@mc.duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER NETWORK ROP_message

19 (b) (6) The pt's follow-up window will open w/in the next month & final ROP status has

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		not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Higgins, Rosemary (NIH/NICHD) [E]

From: Bridge, Renee <rbridge@ucsd.edu>
Sent: Wednesday, June 17, 2009 7:15 PM
To: Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

I got some info from Sharp today and entered it. The baby has had many eye exams and is still being followed, but I know the baby has passed 55 weeks. Thanks Renee _____
From: Rich, Wade
Sent: Wednesday, June 17, 2009 11:11 AM
To: Bridge, Renee
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 17, 2009 11:11 AM
To: Finer, Neil; Rich, Wade
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose
CENTER

NETWORK

ROP_message

22

(b) (6)

No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, June 17, 2009 6:36:06 PM

workin' on it.
ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

06/17/2009 02:11 PM

To "Ronald GOldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Melody B Lohmeyer" <lohme001@mc.duke.edu>, <Kimberley.fisher@duke.edu>, <gloria.siaw@duke.edu>, <cotte010@mc.duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: SUPPORT
Date: Wednesday, June 17, 2009 6:06:36 PM

yes -Kim Lutz,RN (b) (6) .
ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
06/17/2009 05:05 PM

To "Ronald GOldberg" <goldb008@mc.duke.edu>
cc
Subject FW: SUPPORT

Do you have a new FU coordinator?
Thanks
Rose

From: Melody B Lohmeyer [mailto:lohme001@mc.duke.edu]
Sent: Wednesday, June 17, 2009 5:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

Hi Rose,
Hope you are having a great summer. I apologize for not sending you this e-mail sooner. I know Kathy Auten spoke with you at SPR about my leaving the position of Nurse Clinician for Neonatology at Duke. I am (b) (6) I have worked at Duke for 26 yrs and in the Division for 17 yrs. I have had a wonderful career at Duke. I have enjoyed working with you and everyone in the network and on the many projects. I wish you all the best. Melody

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

To "Ronald GOldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Melody B Lohmeyer" <lohme001@mc.duke.edu>,

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06/17/2009 02:11 PM

<Kimberley.fisher@duke.edu>, <gloria.siaw@duke.edu>, <cotte010@mc.duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@pwpu.edu; "Nancy Newman"; bss5@pwpu.edu
Cc: "Gantz, Marie"
Subject: RE: SUPPORT
Date: Wednesday, June 17, 2009 3:16:24 PM

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rescheduled AGAIN for (b) (6)

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Gratton, Teresa (grattotl)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Missing SUPPORT data
Date: Wednesday, June 17, 2009 2:21:18 PM

Rose ..... We just received correspondence from you regarding missing SUPPORT data but you listed ID #'s that are not for our
Center, #11. You referenced Ctr #12 but sent to Kurt, Kim, Cathy and I.

I think the message was an error sent to us.

We do not have any infants entered into SUPPORT, here in Cincinnati, with those numbers.

Thanks.

Tari

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing Outcomes
Date: Wednesday, June 17, 2009 1:31:58 PM
Attachments: Infants with missing outcomes 06-17-09.xls

Rose,

Attached is the list of SUPPORT patients who are missing outcomes this week.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
12		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
22		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
24		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Antenatal Consent Paper 6_15 .doc
Date: Tuesday, June 16, 2009 9:42:34 AM
Attachments: Antenatal Consent Paper 6_15 .doc

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 16, 2009 6:38 AM
To: Rich, Wade
Subject: RE: Antenatal Consent Paper 6_15 .doc

It is a word document - can you resend?

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Tuesday, June 16, 2009 9:02 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Antenatal Consent Paper 6_15 .doc

I think it is in 'web view'. Change to 'print view'
Wade

On Jun 16, 2009, at 5:34, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

Wade
I don't see the list of references - can you attach?
Thanks
Rose

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Monday, June 15, 2009 1:58 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Antenatal Consent Paper 6_15 .doc

Rose,

I made some changes right after I sent this, if you have not already sent it out.

wade

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

Wade Rich BSHS, RRT[1], Kathy Auten MSHS[2], Marie Gantz PhD[3], Ellen Hale RN,BS[4], Angelita Hensman RNC[5], Nancy Newman BA, RN[6], and Neil N Finer, MD[1] on behalf of the NICHD Neonatal Research Network

[1] UCSD Medical Center, San Diego, CA; [2]Duke University, Durham NC, [3]Research Triangle Institute, RTP, NC, [4]Emory University, Atlanta GA, [5]Women' and Infant's Hospital, Providence, RI[6]Case Western University, Cleveland OH

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Keywords: Informed Consent, Antenatal, Neonatal

The authors have no financial disclosures or conflicts of interest.

ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled. Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the

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study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to

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the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

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2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the ability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways as shown in Table 1. Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to

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antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance (p=0.0011) and to have received prenatal care (p=0.0039), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, p<0.0001) (Table 2).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers belonged to a second maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

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Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Our study demonstrates that requirement for antenatal consent results in the recruitment of infants that may not be representative of the population being studied. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[6] However, these controls only

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protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[7,8] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [9] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [10] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[11] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [14] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of the Zupancic trial, which took place in a country with universal healthcare, all of these reports of selection bias point toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up

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excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[15], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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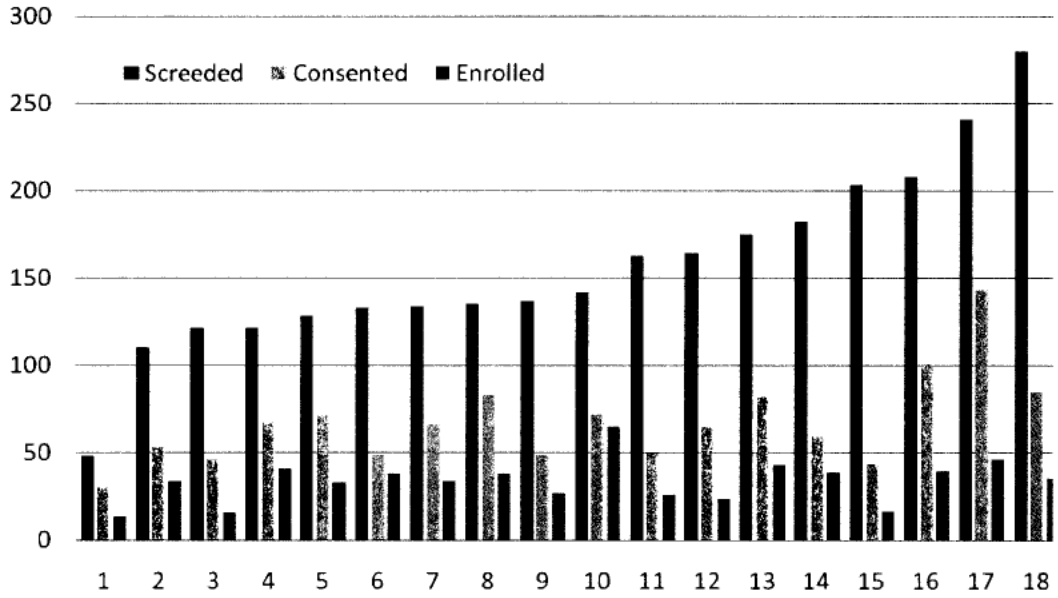

Figure 1. Women who were screened, consented, and enrolled by Center

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 1 Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039

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No Antenatal Steroids	3.8	15.7	<.0001

Table 2. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 2 Reasons for not approaching mothers for consent.

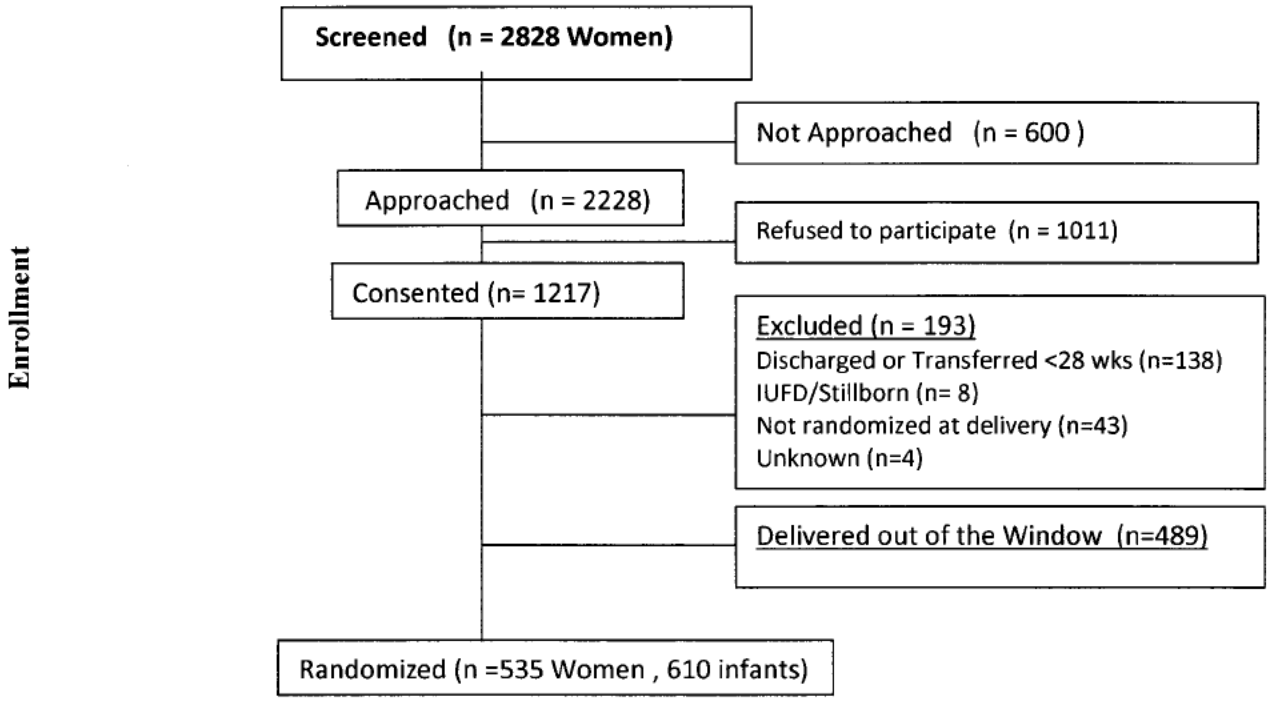

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Antenatal Consent Paper 6_15 .doc
Date: Monday, June 15, 2009 1:57:49 PM
Attachments: Antenatal Consent Paper 6_15 .doc

Rose,

I made some changes right after I sent this, if you have not already sent it out.

wade

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled. Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the

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study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to

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the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

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2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the ability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways as shown in Table 1. Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to

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Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers belonged to a second maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

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Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Our study demonstrates that requirement for antenatal consent results in the recruitment of infants that may not be representative of the population being studied. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for all eligible infants will help us understand whether similar reduction in enrollment occurs when the burden of consent is added to these trials and whether the enrolled infants are representative of the true eligible population.

Blinding and randomization have always been the benchmarks for protecting trials from bias. Investigators have shown that trials in which allocation to a study group is well concealed more accurately reflect the true study effect than those not well concealed.[6] However, these controls only

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protect the trial from internal bias. Manning and Silverman have voiced concerns about selection bias, stating that a disproportionate number of vulnerable and deprived families are involved in clinical research.[7,8] Harth and Thong questioned parents who had volunteered in an asthma trial in Australia and concluded that volunteering parents were "significantly more socially disadvantaged and emotionally vulnerable." [9] In a study of recruitment and retention of premature infants into an early intervention program, Constantine et al found significant enrollment bias in this direction related to race, weight and site. [10] Zupancic et al. analyzed three postnatal trials in Canada, which has universal healthcare and other social benefits, and found no significant socio-economic difference between those who consented when compared with those who did not.[11] Mitchell and Kline, on the other hand, showed a significantly greater proportion of African-Americans, uninsured patients, and Medicaid recipients in the non-participant group in a minimal risk emergency department study.[12] Aagaard-Tillery and the NICHD Maternal Fetal Medicine (MFM) network found that blacks and Hispanics were significantly less likely to allow use of their genetic samples for future studies.[13]

Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [14] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of the Zupancic trial, which took place in a country with universal healthcare, all of these reports of selection bias point toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up

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excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[15], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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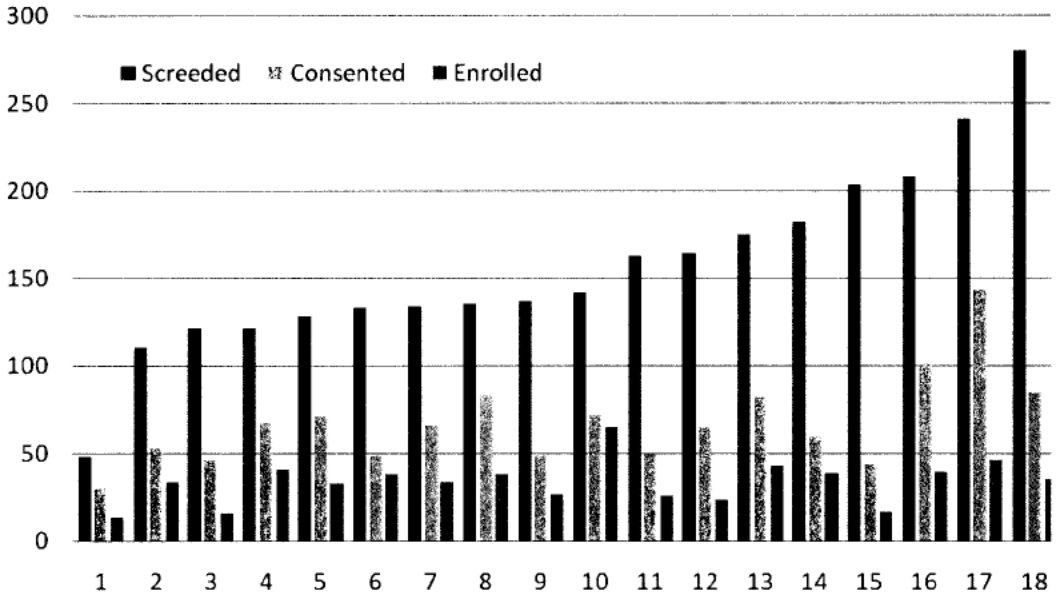

Figure 1. Women who were screened, consented, and enrolled by Center

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 1 Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039

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No Antenatal Steroids	3.8	15.7	<.0001

Table 2. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 2 Reasons for not approaching mothers for consent.

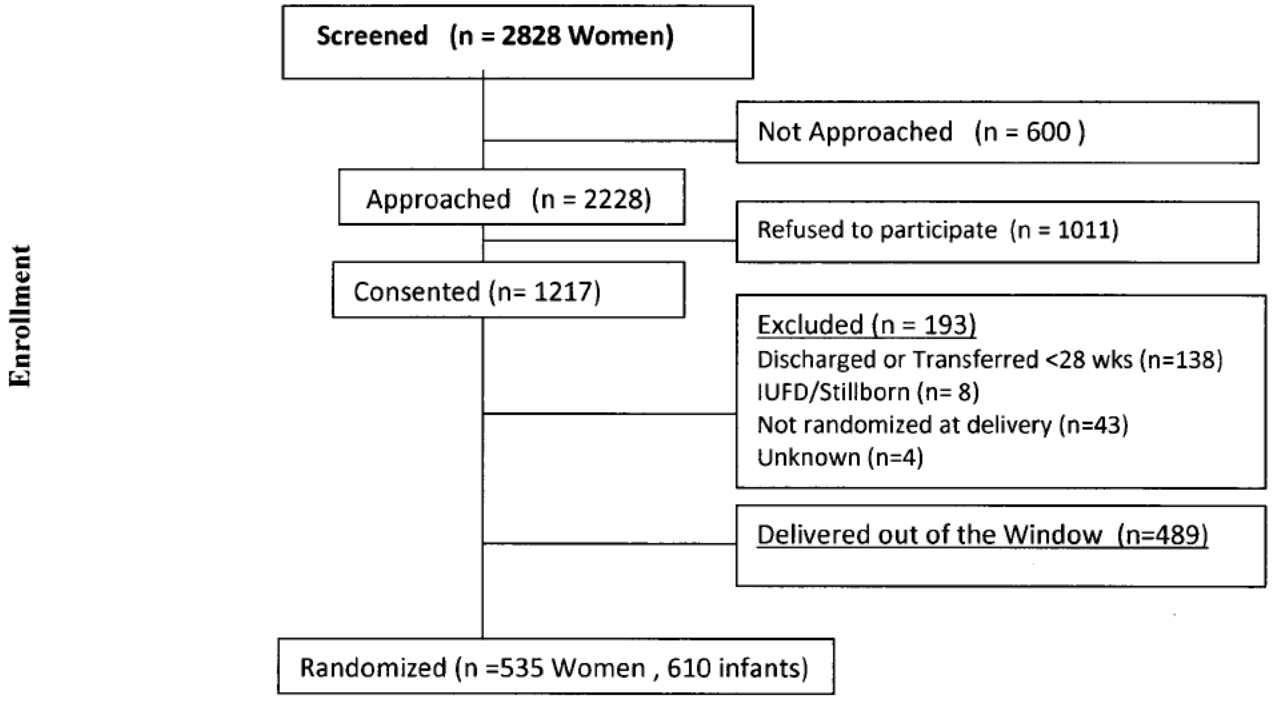

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: Antenatal Consent Paper 6_15 .doc
Date: Monday, June 15, 2009 1:11:38 PM
Attachments: Antenatal Consent Paper 6_15 .doc

Hi Rose,

Attached please find the antenatal consent paper for review by the committee.

wade

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Antenatal Consent in a Large Multicenter Trial – At What Cost?

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ABSTRACT

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Objective:

This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network (NRN) SUPPORT trial and to better predict the time required for recruitment into a complex interventional trial requiring antenatal consent.

Design/Methods:

A data form was designed to obtain information about eligible mothers who were available and approached at each center, to determine who approached them, how often they were approached, the duration of each contact, whether consent was obtained and if the infant(s) was enrolled. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database. These data were used to identify infants who were eligible but not approached or enrolled.

Results

2828 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2228 were approached for informed consent. The most common reasons for not approaching mothers included fetal abnormalities, active labor and language barriers. A study coordinator/research nurse made 75% of all approaches. For 77% of those approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). Estimated GA at time of screening was not different for those who consented versus those who did not. Seven percent of those approached were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2228 mothers approached, 1217 gave consent. Five hundred seventy-eight of those consented delivered 655 infants within the study window, and 535 of these delivered 610 infants that were enrolled. Forty-five consented infants born in the GA window were not enrolled. Only 19% of screened women delivered infants subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use < 30 minutes to obtain consent. A significantly higher proportion of infants who delivered in the

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study window but were not enrolled in SUPPORT had no exposure to antenatal steroids compared with infants who were enrolled. (15.7 vs. 3.8% p<.0001). The difference in lack of antenatal steroid exposure was even greater for the infants of approached vs. non-approached women (3.4 vs. 20.3%, p<.0001).

Conclusions:

In a complex interventional trial of preterm infants requiring antenatal consent, more than 5 women were identified as likely to deliver a baby in the window for each one who delivered an infant enrolled in the trial. Extrapolating these data to the entire SUPPORT trial suggests that over 2400 hours were spent screening greater than 6000 women to enroll 1317 infants in the trial. The differences between enrolled versus non-enrolled infants highlight the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent.

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Introduction:

The process of informed consent was established to ensure that subjects enrolled in research trials were appropriately informed as to the risks and benefits of the trial, came to the trial voluntarily, and represented an accurate cross-section of all subjects who would potentially receive benefit from or undergo the risks of the studied intervention. Traditionally, this consent is obtained directly from the subject when they are in condition to understand and participate in the process. In conducting trials on infants who will receive an intervention at or near the time of birth, the process requires approaching families prior to delivery to provide consent for their infant(s).

Funding for clinical trials sponsored by federal agencies and industry is often based on a model of capitation where a site is paid based on the number of subjects enrolled and some pre-calculated screening time. However, because prospective data comparing the number of families who are approached in the antenatal period to the number of infants who are actually enrolled have not previously been available, the current model may not adequately account for time spent by study staff to screen, approach and enroll all eligible subjects.

Early enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) demonstrated that antenatal screening and consent were labor intensive and that actual patient enrollment numbers differed significantly from the screening and consent rates. Thus, this secondary study was designed to evaluate the antenatal screening and consent process to determine the factors that contribute to successful enrollment of patients in a complex trial conducted by an experienced multi-center trials network.

Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in the multi-center Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Data for this study were collected during the

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last half of the NRN SUPPORT trial. The SUPPORT trial was designed to compare the use of early CPAP initiated in the delivery room to early intubation and surfactant given within the first hour of life, and to compare randomization to 2 different target SpO2 ranges during receipt of supplemental oxygen up to 36 weeks post menstrual age (PMA). Eligible infants were 24 0/7ths to 27 6/7ths weeks gestational age (GA) without known malformation for whom full postnatal treatment was expected.

Eligible subjects for the antenatal consent secondary study were those women who the Obstetrical/Perinatal staff felt were likely to deliver in the SUPPORT gestational age window. Clinical data were collected by trained research coordinators, and all analyses were performed at a central data coordinating center (DCC) (RTI International, Research Triangle Park, NC). Research staff self-reported study data using a one page data collection form. If the parent(s) were not approached for consent, the reason they were not approached was recorded. If they were approached, the staff recorded the total number of times the parent(s) were approached, the number of such attempts which were made by the research coordinator/RN, and whether OB permission was obtained to approach for antenatal consent. As a neonatal consult is often performed on this population, staff recorded whether a consult was performed, whether the consent was discussed during the consultation, and whether consent was obtained at the time of the consult. In some centers the Institutional Review Board required a consult be completed prior to consent, so this was also recorded. Women who were approached for SUPPORT were asked if they were approached for participation in any other studies either for themselves or their infants. Finally, the study staff was asked to estimate the time required to obtain a decision regarding consent.

Data were collected at each of the 18 NICHD NRN centers until fifty mothers had delivered within the window at the center. Data forms were keyed by the centers and transmitted electronically to the DCC. Infants born at Network centers who delivered in the SUPPORT window were entered into the NRN Generic Database (GDB) which, before 2008, collected delivery and demographic data on infants between 401 and 1500g inclusive birth weight who were inborn at NRN centers or admitted to

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the NICU within 14 days of age. Beginning in 2008, the database collected infants who were 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 and 28 6/7 weeks (<29 weeks) inclusive gestational age. GDB data were used to evaluate whether infants enrolled in the SUPPORT trial represented the entire eligible Network population.

To determine the representativeness of the population enrolled in the SUPPORT trial, data from the GDB were obtained for those infants born at NRN centers during the period of SUPPORT trial enrollment who qualified to participate in SUPPORT. This information included whether prenatal care was obtained, the use of antenatal steroids and demographic data. These data were compared for infants who were or were not enrolled in SUPPORT to assess whether the trial had enrolled a representative sample of the available population. In addition, comparisons were made between eligible infants whose mothers were or were not approached for SUPPORT.

We performed bivariate statistical analyses using Chi-Square and Student's t-tests. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered statistically significant. This trial was approved by the Institutional Review Boards of all participating centers as well as that of RTI.

Results

Between October 2005 and February 2009, a total of 2828 women were identified at 18 NRN centers as being at risk for delivering a premature infant between 24 to 27 6/7 wks GA and otherwise eligible for participation in the SUPPORT trial. Two additional NRN centers did not participate in the antenatal consent trial and 4 who did participate did not identify 50 eligible women between the start of data collection for the antenatal consent study and the end of the SUPPORT trial. Four centers identified more than 50 women (mean 82) before they were informed that they could stop collecting data. All data collected by participating centers have been included in this analysis. Results of an analysis using only the first 50 women from the centers that over-enrolled were not significantly different. Data for screening, enrollment and consent by center are presented in Figure 1.

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2228 women were approached for informed consent. The two most frequent reasons for not attempting to obtain a consent were early discharge and a lack of time prior to delivery (Table 2). Common choices within the "other" category in the table were early discharge, the ability of the mother to give consent, fetal abnormalities, and language barriers that made informed consent impossible. Reasons mothers were considered unable to give consent included being in active labor, being too young, and having either a mental or physical health issue which precluded them being approached. A study coordinator or research RN made 75% of all approaches. For 77% of those women approached, consent was attempted < 3 times. (Overall mean 2.0 +/- 1.2). The frequency of approaches ranged from 1 (n=900) to 11 (n=2) times. The median time spent to obtain a decision regarding consent was less than 1 hour regardless of the decision. The estimated GA at time of screening was not significantly different for those who consented versus those who did not. Of the 2228 mothers approached, 1217 gave consent, 578 subsequently delivered 655 infants within the SUPPORT study window, and 535 delivered 610 infants who were enrolled (Figure 2). Forty-five consented infants born in the GA window (7%) were not enrolled, usually due to lack of staffing, equipment, or time. Only 19% of those mothers screened delivered infants who were subsequently enrolled in the study. A neonatal consult was performed in 70% of cases. There was a significant relationship between performing a neonatal consult and obtaining consent ($p < .0001$), but consent was only obtained during the consult 12% of the time. Centers that were also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to require less than 30 minutes to obtain a consent decision. The median time spent to obtain a decision regarding consent for all centers was less than 1 hour regardless of the decision.

Infants of non-approached and approached mothers were different in several important ways as shown in Table 1. Infants of approached mothers were more likely to be non-Hispanic white ($p<0.0001$); the mothers were more likely to be older ($p=0.0210$) and to have a high school education ($p<0.0001$), medical insurance ($p<0.0001$), and at least one PNC visit ($p<0.0001$). A significantly higher proportion of infants born in the study window whose mothers were not approached for SUPPORT had no exposure to

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antenatal steroids compared with infants whose mothers were approached (20.3% vs 3.4%, p<.0001). Maternal gravidity and parity were not significantly different between these groups.

Infants who were enrolled in SUPPORT and those who were not enrolled were also significantly different. Non-enrolled infants had mothers who were significantly less likely to have insurance (p=0.0011) and to have received prenatal care (p=0.0039), and were over 4 times more likely to have gone without antenatal steroids (15.7% vs. 3.8%, p<0.0001) (Table 2).

Discussion:

To our knowledge this is the first neonatal study to evaluate the time and work required to approach and obtain consent from parents for the enrollment of their premature infants who at the time of the consent were not yet born. Our results reveal that 5 families needed to be identified and screened for every one that had an infant successfully enrolled. Only 47% of women from whom consent was obtained went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.7) yields a value for coordinator time required to obtain an enrolled infant at between 1.8 and 3.7 hours. This includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

Morley et al reviewed parental willingness to participate in multiple trials in the neonatal period and found that most (74%) were willing to allow their baby to participate in multiple trials. [1] We had concerns that the burden of being approached for multiple trials, especially since 5 centers belonged to a second maternal/fetal research network, would affect the enrollment in SUPPORT. We found that only 8% of women had been approached for another trial at the time of the SUPPORT consent discussion, probably because it was an antenatal consent and the window was early in gestation.

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Because of the unique attributes of the NRN, we were able to obtain demographic data from the GDB for infants who were delivered in the SUPPORT window but were not enrolled in the study. Thus, we were able to compare infants who were vs. were not enrolled and those whose mothers were vs. were not approached. These groups differed in a number of significant areas. Most importantly, infants born to women who were not approached for consent were almost 6 times more likely not to have been exposed to antenatal steroids, an intervention known to be associated with better short and longer term outcomes for preterm infants. [2] They were also more likely to be more immature and their mothers were significantly less likely to have insurance and to have received prenatal care.

In a review of NIH funded interventional randomized controlled trials, Charlson and Horwitz found that only half such trials kept any data on subjects who were eligible but not enrolled, and for those trials which did keep data only 27% of eligible non-enrolled subjects were a result of subject refusal.[3] The Consolidated Standards for Reporting of Trials (CONSORT) is a document created with the intent of standardizing items reported in trial publications, including a checklist for necessary items and a flow chart of participants.[4,5] The standards require the quantifying of eligible populations but make no such requirement for identifying the demographics of this group or its similarity to the enrolled or consented populations. Research from the California Department of Health Services reviewed the effect of the introduction of tandem Mass Spectrometry (MS/MS) to the California Newborn Screening program.[6] This involved another test on an already collected blood spot, for which it was decided informed consent was necessary. They found that the burden of adding informed consent to the screening process resulted in only 50% of infants being screened for the new test. Twenty one percent of participating hospitals did not offer the screening because of the burden of providing informed consent. It is very possible that failure rates for enrollment of infants in trials that require consent in the antenatal period is much higher than is currently believed. Following the CONSORT standards in all antenatal consent trials, both consented and waived, and obtaining basic demographic information for

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Glassberg, Luce and Matthay analyzed the screening and enrollment of a trial of acute lung injury in two San Francisco hospitals, one an academic referral center and the other the public hospital for the city. [15] The percentage of screened infants enrolled was nearly 3 times higher in the academic center, a statistically significant difference ($p<.0001$). All of the centers in our trial were academic centers, but many included a relationship with a non-academic center. With the exception of Zupancic, which took place in a country with universal healthcare, all of these reports of selection bias point

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toward the need to find a better method of enrolling truly representative populations for trials evaluating better practices.

The bias in our analysis would suggest that under privileged subjects were less likely to participate. Because this trial enrolled subjects from all socio-economic groups at 18 academic centers with long-term randomized trial experience, it is not likely that the bias involved represents an intention to include or not include any group. The logical conclusion is that the many subjects who ended up excluded from this trial, despite the significant time and effort spent by the coordinators to include them, represent a failure of, or an innate problem with, the antenatal-consent process itself. Our observations, along with previous experience in a trial of a delivery room intervention[16], suggest that it is appropriate from an ethical perspective to allow trials that compare standard of care interventions to waive the consent process until after birth. This would ensure that the infants enrolled in such a trial do not differ significantly from the overall eligible population and insure the generalizability of the results.

Conclusion

Our prospective analysis of the process of antenatal consent enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, that actual patient enrollment numbers may be significantly lower than screening and consent rates, and that the population studied may not be representative of the total eligible population. In this complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Antenatal steroid use was significantly higher among infants enrolled in the SUPPORT study compared to those who were eligible but not enrolled, with a similar difference between infants born to approached and non-approached women. Along with quantifying the time and expense of antenatal consent, these observations point out the difficulties in attempting to recruit a representative population for prospective trials requiring antenatal consent and suggest that greater use of waiver of consent for trials that are low risk may be appropriate for future studies.

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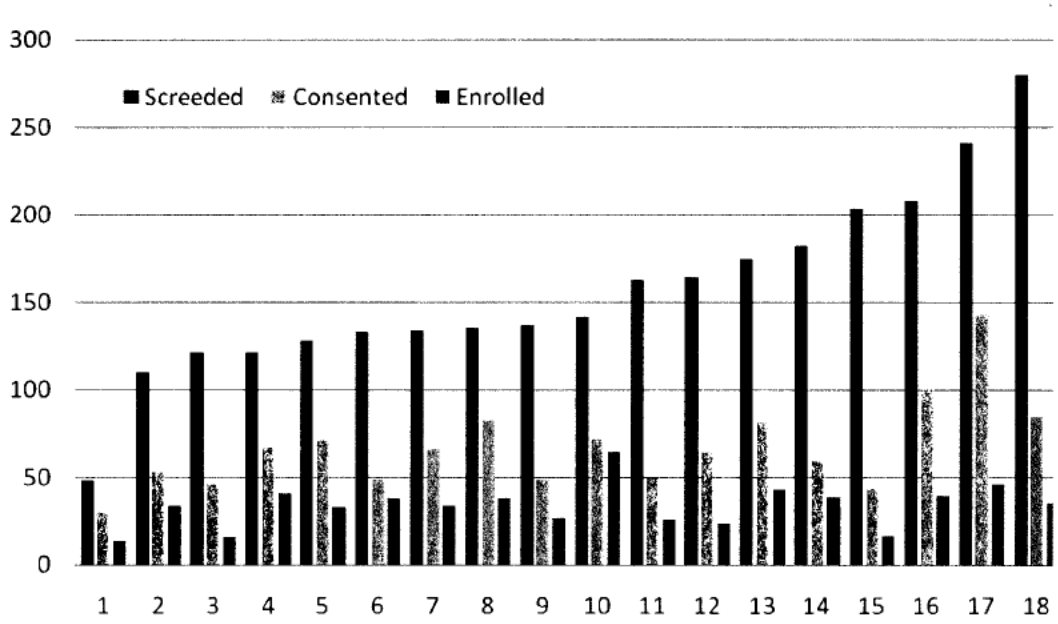

Figure 1. Women who were screened, consented, and enrolled by Center

	Infants whose Mothers were Approached N=2080	Infants whose Mothers were Not Approached N=2173	p Value
Maternal age (Mean ± SD)	27.4 ± 6.4	27.0 ± 6.8	0.0210
White-Non Hispanic	41.1	34.3	<.0001
Gravidity (Mean ± SD)	2.7 ± 2.0	2.9 ± 2.1	0.0546
Parity (Mean ± SD)	2.2 ± 1.4	2.3 ± 1.5	0.0505
≥ HS Education	75.1	68.8	<.0001
Self Pay/Uninsured	6.3	10.0	<.0001
At Least 1 PN Visit	96.8	92.2	<.0001
No Antenatal Steroids	3.4	20.3	<.0001

Table 1 Demographic data comparing infants born to women who were approached for consent in the SUPPORT trial and who delivered in the GA window with GDB infants who were eligible for the trial but whose mothers were not approached.

	Infants enrolled in SUPPORT N=1317	Infants not enrolled N=2936	p Value
Maternal age (Mean ± SD)	27.1 ± 6.4	27.3 ± 6.7	0.4834
White-Non Hispanic	39.7	36.7	0.0580
Gravidity (Mean ± SD)	2.8 ± 2.0	2.8± 2.0	0.9734
Parity (Mean ± SD)	2.3± 1.5	2.3 ± 1.5	0.7198
≥ HS Education	73.8	71.0	0.1093
Self Pay/Uninsured	6.1	9.1	0.0011
At Least 1 PN Visit	96.0	93.8	0.0039

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No Antenatal Steroids	3.8	15.7	<.0001

Table 2. Demographic data comparing infants enrolled in SUPPORT vs GDB infants who were eligible but not enrolled.

Reason	N	Percent of Total
Active Labor	69	11.6
Insufficient time	119	20.0
Night, Weekend Holiday	37	6.2
Consult not done	17	2.9
Not aware of admission	35	5.9
Other	319	53.5

Table 2 Reasons for not approaching mothers for consent.

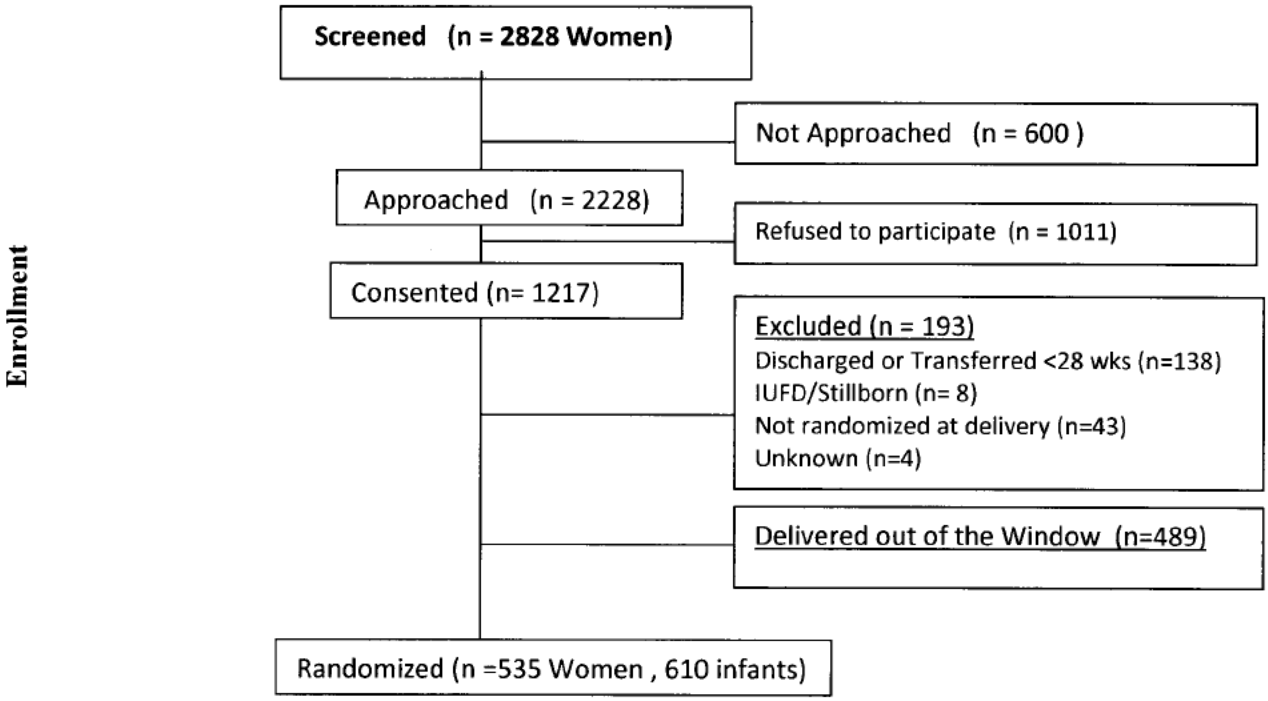

Figure 2. Modification of the CONSORT diagram showing the flow of participants through the enrollment stage of a randomized trial using Antenatal Consent.

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CSR	Tian, Biao	**NIA**	Bernard, Marie	**NIDDK**	Jones, Teresa
			Joseph, Lyndon		
NCATS	McInnes, Pamela			**NIMH**	Juliano-Bult, Denise
		NIBIB	Peng, Grace		Shelli Avenevoli
NCCIH	Khalsa, Partap				
	Lohman, Karin	**NICHD**	Spong, Cathy		
	Shurtleff, David		Freund, Lisa	**NINDS**	Bellgown, Patrick
	Reider, Eve		Meikle, Susan		Chen, Daofen
			Parisi, Melissa		Finkelstein, Robert
NCI	O'Mara, Ann		Maholmes, Valerie		Jakeman, Lynn
	Rowland, Julia				
		NIDCD	Cooper, Judith	**NINR**	Knebel, Ann
NEI	Greenwell, Tom		Shekim, Lana		Tully, Lois
	Wiggs, Cheri				
		NIAMS	Boyce, Amanda	**OD**	Ershow, Abby
NHLBI	Fleg, Jerome		Chuck Washabaugh		
			McGowan, Joan		
			Panagis, James		

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; "nancy newman"
Cc: "Gantz, Marie"
Subject: RE: SUPPORT
Date: Friday, June 12, 2009 3:59:55 PM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 05, 2009 12:16 PM
To: mcw3@cwru.edu; Bonnie Siner; nancy newman
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

THIS IS TERRIFIC GIVEN YOUR OUTSTANDING RECRUITMENT!!!

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	Rescheduled AGAIN for (b) (6)
		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	Complete and entered.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline
Subject: RE: SUPPORT
Date: Tuesday, June 09, 2009 4:05:36 PM

Hi. See below-

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.1121 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 05, 2009 12:23 PM
To: Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn; Hamer, Faithe Angeline
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
12	[redacted]	The patient is within their Fol-up window and final ROP status has not been reported. Follow up visit June 23rd
12	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.--I am looking into this
CENTER	NETWORK	BPD_message
12	[redacted]	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.-Data has been transmitted
12	[redacted]	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.-Infant still in hospital
12	[redacted]	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.- Infant still in hospital
12	[redacted]	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.- Infant still in hospital
CENTER	NETWORK	FU_message
12	[redacted]	FU window has closed but NF08a has not been completed.- Visit on May 13th-waiting on return of Bayley info from examiner-you may expect soon-
12	[redacted]	FU window has closed but NF08a has not been completed.- Visit on May 13th-waiting on return of Bayley info from examiner-you may expect soon

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From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, June 08, 2009 1:28:01 PM

No updates on (b) (6). Called her last week and she said to call her in 2 weeks. I will attempt to schedule again next week.

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713.500.6813 (office)
713.500.5794 (fax)
713.760.(b) (6) (pager)
Margaret.L.Poundstone@uth.tmc.edu (e-mail)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 05, 2009 11:25 AM
To: Tyson, Jon E; Kennedy, Kathleen A; Mcdavid, Georgia E; Evans, Patricia W; Poundstone, Margaret
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Friday, June 05, 2009 11:47:44 PM

Ok with me

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 04, 2009 2:50 PM
To: Seetha Shankaran; kurt.schibler@cchmc.org; Wally Carlo, M.D.; Ronald Goldberg; Frantz, Ivan; Bell, Edward; Kristi Watterberg
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Request for SUPPORT forms

Hi, Let me know if this is ok or not.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 28, 2009 11:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; 'Cunningham, Meg'; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

Hi
Dr. Finer has requested permission to use the SUPPORT forms and manual for his R34 clinical trial planning grant for the PreSox trial sponsored by NICHD. Please send me a yes/no vote by June 2.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kish Wattinberg"; "Corea Lacy"
Cc: "Davis, Maria"
Subject: SUPPORT
Date: Friday, June 05, 2009 12:36:57 PM
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
26	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
26	(b) (6)	Infant has been discharged and was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is not entered.

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "bradley.yoder@hsc.utah.edu"; "Roger.Faix@hsc.utah.edu"; "Karen.Osborne@hsc.utah.edu"; "abodnar@utah.gov"
Cc: "Gantz, Marie"
Subject: SUPPORT
Date: Friday, June 05, 2009 12:35:45 PM
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	BPD_message
25	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing Outcomes
Date: Friday, June 05, 2009 12:01:30 PM
Attachments: Infants with missing outcomes 06-04-09.xls

Rose,

Attached is the list of SUPPORT infants missing outcomes this week.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
12		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		The patient is within their Fol-up window and final ROP status has not been reported.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
26		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Request for SUPPORT forms
Date: Thursday, June 04, 2009 6:50:35 PM

---

ok with us.
ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

06/04/2009 03:50 PM

To "Seetha Shankaran" <sshankar@med.wayne.edu>, <kurt.schibler@cchmc.org>, "Wally Carlo" <wcarlo@peds.uab.edu>, "Ronald Goldberg" <goldb008@mc.duke.edu>, "Frantz, Ivan" <ifrantz@tuftsmedicalcenter.org>, "Bell, Edward" <edward-bell@uiowa.edu>, "Kristi Watterberg" <KWatterberg@salud.unm.edu>
cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>
Subject FW: Request for SUPPORT forms

Hi, Let me know if this is ok or not.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 28, 2009 11:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; 'Cunningham, Meg'; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

Hi

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Dr. Finer has requested permission to use the SUPPORT forms and manual for his R34 clinical trial planning grant for the PreSox trial sponsored by NICHD. Please send me a yes/no vote by June 2.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Request for SUPPORT forms
Date: Thursday, June 04, 2009 5:43:21 PM

Hi Rose,
Yes, this is OK.
Kurt

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 6/4/2009 3:50 PM >>>
Hi, Let me know if this is ok or not.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 28, 2009 11:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; 'Cunningham, Meg'; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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Thanks
Rose

Rosemary D. Higgins, MD

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Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Frantz, Ivan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, June 04, 2009 3:57:14 PM

Seems ok to me.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 6/4/2009 3:54 PM
To: Frantz, Ivan
Subject: RE: Request for SUPPORT forms

Yes, but they would likely acknowledge the nrn (they need access to the forms)

From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Thursday, June 04, 2009 3:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms

I thought they had clraified that they did not want to use the forms, but only wanted to review them to create a new form for ROP for their new study.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 6/4/2009 3:50 PM
To: Seetha Shankaran; kurt.schibler@cchmc.org; Wally Carlo; Ronald Goldberg; Frantz, Ivan; Bell, Edward; Kristi Watterberg
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Request for SUPPORT forms

Hi, Let me know if this is ok or not.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 28, 2009 11:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; 'Cunningham, Meg'; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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Thanks

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Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, June 04, 2009 3:54:41 PM

Okay with me
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 04, 2009 3:50 PM
To: Shankaran, Seetha; kurt.schibler@cchmc.org; Wally Carlo; Ronald Goldberg; Frantz, Ivan; Bell, Edward; Kristi Watterberg
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Request for SUPPORT forms

Hi, Let me know if this is ok or not.

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Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 28, 2009 11:08 AM
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

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Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; 'Cunningham, Meg'; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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From: Gantz, Marie
To: Vaucher, Yvonne
Cc: Betty_Vohr@brown.edu; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik
Subject: RE: Support FUP
Date: Thursday, June 04, 2009 1:01:42 PM
Attachments: Bayley II vs III distributions 06-02-09.rtf

Yvonne,

See below for answers to your questions.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 29, 2009 12:26 AM
To: Gantz, Marie
Cc: Betty_Vohr@brown.edu; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik
Subject: RE: Support FUP

Marie,

How are we using the language scores? How is the Bayley III composite score (cognitive + language) derived? Could we use the combined cognitive + language scores for the NDI? The cognitive composite is a much more normal distribution. The Bayley III language scores are skewed downward.

MG: Right now, the Bayley III language score is not incorporated into our network definition of NDI. Your questions about combining the cognitive and language scores would be better answered by Betty, as I am not familiar with how the scores are derived, and I believe that any change to the NDI definition would have to be discussed by the follow up subcommittee.

What is the difference in sample size needed if NDI is the primary outcome using cognitive scores < 70 from the Bayley IIII instead of the Bayley II?
What is the effect on sample size needed if we used the Bayley II MDI or Bayley III cognitive score <70 alone as opposed to using it as a component of NDI?
What sample size is needed if we compare cognitive scores < 85 (< 1 SD below the mean), alone and as a component of NDI?

MG: The sample size for the SUPPORT trial were based on a conservative event rate of 50% (because when there are multiple outcomes the one with prevalence nearest 50% drives the sample size requirement) and the sample size was then increased to account for the randomization of multiples to the same group and for loss to follow up. So, the sample size calculations were not influenced by the distribution of the Bayley II scores and would not be impacted by a switch to the Bayley III.

For Support, were the sample size adjustments of 12% for multiples (randomized together) and 17% for LTFU used to arrive at a final sample size of 1310? How is the multiples adjustment derived? How would the sample size adjustment be changed if multiples were randomized separately?

MG: The sample size adjustments for multiples and loss to FU were used to arrive at the final sample size of 1310. The multiples adjustment was based on the multiples rate in the GDB. Without both adjustments, the sample size would have been about 1000.

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Although the NDI results using the Bayley III cognitive or composite scores will not be comparable to previous studies that used the Bayley II MDI, won't the relative differences between control and intervention arms within an individual RCT using the Bayley III be similar?

MG: The differences would be similar unless the intervention had a different impact on the Bayley III outcome than it had on the Bayley II outcome.

How does using a cutoff of below 85 rather than below 70 affect comparison of the Bayley II vs III? According to the NRN% Distribution for Bayley II MDI and Bayley III Cognitive score (12/17/08) accompanying the Technical Report, there are substantially more children on the Bayley II below the 85 cutoff. How much closer are the curves if the Bayley III language scores are added to the cognitive scores?

MG: See attached for frequencies of Bayley II and III scores where you can see the percent of children with scores below 70 and below 85. These data are for GDB infants born in 2004-2007 who have either the Bayley II or III.

Please send the distribution statistics for the Bayley II MDI and PDI in the same format as the distribution scores you sent Wade Rich for the Bayley III (Mean, SD, Median, Modes, Skewness, quartiles, etc.....).

MG: See attached for distributions of the Bayley II and III scores.

Thanks for your helping me understand this.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, May 26, 2009 7:05 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

The sample size calculations in the SUPPORT protocol also mention the follow up outcome of death or NDI, though the primary outcomes are death or BPD and death or ROP. (Page 24 of the protocol states: "Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome.") Of course, these were based on the Bayley II and may not obtain for the Bayley III. I am happy to discuss this issue as well.

Thanks

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Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 26, 2009 9:57 AM
To: Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik;; Finer, Neil
Subject: RE: Support FUP

Yvonne
Marie Gantz is the statistician for SUPPORT. The sample size for SUPPORT was determined based on the primary outcomes of BPD/ROP/ and death. FU was originally listed as a secondary outcome.

Confidentially, children are scoring better on the Bayley III as opposed to the Bayley II. For an upcoming trial, we are using a cognitive score of < 85 on the Bayley III as one component of neurodevelopmental impairment.

Perhaps we should discuss this one the follow up call scheduled for mid-July?
let me know

Regards
Rose

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 22, 2009 3:08 PM
To: Betty_Vohr@brown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support FUP

Betty and Rose,

As I have not been part of the primary group, who is the best person(s) to talk to at RTI and within our follow-up group about the sample size/Bayley 3 questions for the Support trial so I can best understand the issues?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759

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FAX: 619-543-3812

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Bayley II vs. III by Birth Year
(GDB infants born 2005-2007)

The FREQ Procedure

Table of bayley2 by bayley3			
bayley2(Has Bayley II score(s))	bayley3(Has Bayley III score(s))		
Frequency	No	Yes	Total
No	0	1308	1308
Yes	1953	10	1963
Total	1953	1318	3271

Table of birthyear by bayley2			
birthyear	bayley2(Has Bayley II score(s))		
Frequency	No	Yes	Total
2004	0	1065	1065
2005	132	891	1023
2006	820	7	827
2007	356	0	356
Total	1308	1963	3271

Table of birthyear by bayley3			
birthyear	bayley3(Has Bayley III score(s))		
Frequency	No	Yes	Total
2004	1065	0	1065
2005	882	141	1023
2006	6	821	827
2007	0	356	356
Total	1953	1318	3271

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

	MDI			
FMDI	Frequency	Percent	Cumulative Frequency	Cumulative Percent
49	215	11.00	215	11.00
50	36	1.84	251	12.85
51	3	0.15	254	13.00
52	10	0.51	264	13.51
53	15	0.77	279	14.28
54	20	1.02	299	15.30
55	16	0.82	315	16.12
56	23	1.18	338	17.30
57	22	1.13	360	18.42
58	19	0.97	379	19.40
59	23	1.18	402	20.57
60	13	0.67	415	21.24
61	24	1.23	439	22.47
62	18	0.92	457	23.39
63	35	1.79	492	25.18
64	25	1.28	517	26.46
65	27	1.38	544	27.84
66	17	0.87	561	28.71
67	24	1.23	585	29.94
68	26	1.33	611	31.27
69	34	1.74	645	33.01
70	17	0.87	662	33.88
71	21	1.07	683	34.95
72	19	0.97	702	35.93
73	32	1.64	734	37.56
74	32	1.64	766	39.20
75	30	1.54	796	40.74
76	32	1.64	828	42.37
77	62	3.17	890	45.55
78	27	1.38	917	46.93
79	53	2.71	970	49.64
80	22	1.13	992	50.77
81	65	3.33	1057	54.09
82	40	2.05	1097	56.14
83	50	2.56	1147	58.70

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

MDI				
MDI	Frequency	Percent	Cumulative Frequency	Cumulative Percent
84	50	2.56	1197	61.26
85	48	2.46	1245	63.72
86	53	2.71	1298	66.43
87	45	2.30	1343	68.73
88	36	1.84	1379	70.57
89	34	1.74	1413	72.31
90	34	1.74	1447	74.05
91	51	2.61	1498	76.66
92	38	1.94	1536	78.61
93	31	1.59	1567	80.19
94	35	1.79	1602	81.99
95	36	1.84	1638	83.83
96	34	1.74	1672	85.57
97	22	1.13	1694	86.69
98	24	1.23	1718	87.92
99	13	0.67	1731	88.59
100	26	1.33	1757	89.92
101	19	0.97	1776	90.89
102	15	0.77	1791	91.66
103	23	1.18	1814	92.84
104	10	0.51	1824	93.35
105	11	0.56	1835	93.91
106	15	0.77	1850	94.68
107	12	0.61	1862	95.29
108	13	0.67	1875	95.96
109	11	0.56	1886	96.52
110	9	0.46	1895	96.98
111	4	0.20	1899	97.19
112	4	0.20	1903	97.39
113	9	0.46	1912	97.85
114	4	0.20	1916	98.06
115	4	0.20	1920	98.26
116	4	0.20	1924	98.46
117	2	0.10	1926	98.57
118	1	0.05	1927	98.62

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

MDI				
MDI	Frequency	Percent	Cumulative Frequency	Cumulative Percent
119	3	0.15	1930	98.77
120	1	0.05	1931	98.82
121	3	0.15	1934	98.98
122	1	0.05	1935	99.03
123	6	0.31	1941	99.33
124	2	0.10	1943	99.44
125	2	0.10	1945	99.54
126	1	0.05	1946	99.59
127	2	0.10	1948	99.69
129	1	0.05	1949	99.74
130	3	0.15	1952	99.90
132	1	0.05	1953	99.95
137	1	0.05	1954	100.00

Frequency Missing = 9

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

	PD			
PDD	Frequency	Percent	Cumulative Frequency	Cumulative Percent
49	226	11.67	226	11.67
50	45	2.32	271	14.00
51	13	0.67	284	14.67
52	5	0.26	289	14.93
53	6	0.31	295	15.24
54	5	0.26	300	15.50
55	16	0.83	316	16.32
56	6	0.31	322	16.63
57	9	0.46	331	17.10
58	4	0.21	335	17.30
59	22	1.14	357	18.44
60	3	0.15	360	18.60
61	8	0.41	368	19.01
62	15	0.77	383	19.78
63	16	0.83	399	20.61
64	1	0.05	400	20.66
65	5	0.26	405	20.92
66	16	0.83	421	21.75
67	20	1.03	441	22.78
68	4	0.21	445	22.99
69	5	0.26	450	23.24
70	47	2.43	497	25.67
71	18	0.93	515	26.60
72	5	0.26	520	26.86
73	10	0.52	530	27.38
74	45	2.32	575	29.70
75	37	1.91	612	31.61
76	5	0.26	617	31.87
77	12	0.62	629	32.49
78	61	3.15	690	35.64
79	40	2.07	730	37.71
80	8	0.41	738	38.12
81	14	0.72	752	38.84
82	60	3.10	812	41.94
83	39	2.01	851	43.96

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

	PDI			
(PDI)	Frequency	Percent	Cumulative Frequency	Cumulative Percent
84	16	0.83	867	44.78
85	31	1.60	898	46.38
86	94	4.86	992	51.24
87	65	3.36	1057	54.60
88	12	0.62	1069	55.22
89	27	1.39	1096	56.61
90	106	5.48	1202	62.09
91	81	4.18	1283	66.27
92	9	0.46	1292	66.74
93	51	2.63	1343	69.37
94	66	3.41	1409	72.78
95	58	3.00	1467	75.77
96	5	0.26	1472	76.03
97	47	2.43	1519	78.46
98	44	2.27	1563	80.73
99	52	2.69	1615	83.42
100	27	1.39	1642	84.81
101	17	0.88	1659	85.69
102	31	1.60	1690	87.29
103	47	2.43	1737	89.72
104	13	0.67	1750	90.39
105	21	1.08	1771	91.48
106	20	1.03	1791	92.51
107	32	1.65	1823	94.16
108	10	0.52	1833	94.68
109	14	0.72	1847	95.40
110	12	0.62	1859	96.02
111	11	0.57	1870	96.59
112	5	0.26	1875	96.85
113	14	0.72	1889	97.57
114	12	0.62	1901	98.19
115	4	0.21	1905	98.40
116	3	0.15	1908	98.55
117	3	0.15	1911	98.71
118	2	0.10	1913	98.81

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Frequency of Bayley II Scores
(GDB infants born 2005-2007)

The FREQ Procedure

PDI				
PDI	Frequency	Percent	Cumulative Frequency	Cumulative Percent
119	7	0.36	1920	99.17
120	1	0.05	1921	99.23
121	5	0.26	1926	99.48
122	1	0.05	1927	99.54
123	1	0.05	1928	99.59
124	1	0.05	1929	99.64
125	4	0.21	1933	99.85
128	2	0.10	1935	99.95
132	1	0.05	1936	100.00

Frequency Missing = 27

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Frequency of Bayley III Scores
(GDB infants born 2005-2007)

The FREQ Procedure

Cognitive Composite				
NFSBSCC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
51	36	2.74	36	2.74
55	20	1.52	56	4.26
60	22	1.67	78	5.94
61	1	0.08	79	6.01
65	30	2.28	109	8.30
70	56	4.26	165	12.56
75	62	4.72	227	17.28
80	136	10.35	363	27.63
85	150	11.42	513	39.04
90	223	16.97	736	56.01
95	189	14.38	925	70.40
100	147	11.19	1072	81.58
103	1	0.08	1073	81.66
105	103	7.84	1176	89.50
110	71	5.40	1247	94.90
115	34	2.59	1281	97.49
120	14	1.07	1295	98.55
125	9	0.68	1304	99.24
130	7	0.53	1311	99.77
135	2	0.15	1313	99.92
140	1	0.08	1314	100.00

Frequency Missing = 4

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Frequency of Bayley III Scores
(GDB infants born 2005-2007)

The FREQ Procedure

Language Composite				
NEWABSLC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
46	39	3.03	39	3.03
47	10	0.78	49	3.80
49	1	0.08	50	3.88
50	16	1.24	66	5.12
53	8	0.62	74	5.75
56	16	1.24	90	6.99
59	23	1.79	113	8.77
61	1	0.08	114	8.85
62	27	2.10	141	10.95
65	31	2.41	172	13.35
66	1	0.08	173	13.43
68	49	3.80	222	17.24
70	3	0.23	225	17.47
71	55	4.27	280	21.74
73	1	0.08	281	21.82
74	76	5.90	357	27.72
75	1	0.08	358	27.80
77	78	6.06	436	33.85
79	92	7.14	528	40.99
82	3	0.23	531	41.23
83	80	6.21	611	47.44
85	2	0.16	613	47.59
86	91	7.07	704	54.66
88	1	0.08	705	54.74
89	81	6.29	786	61.02
91	95	7.38	881	68.40
94	67	5.20	948	73.60
95	2	0.16	950	73.76
97	70	5.43	1020	79.19
100	61	4.74	1081	83.93
102	1	0.08	1082	84.01
103	4.58	4.58	1141	88.59
106	42	3.26	1183	91.85
107	1	0.08	1184	91.93
109	36	2.80	1220	94.72

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Frequency of Bayley III Scores
(GDB infants born 2005-2007)

The FREQ Procedure

	Language Composite			
NF9ABSLC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
112	14	1.09	1234	95.81
115	15	1.16	1249	96.97
118	15	1.16	1264	98.14
121	10	0.78	1274	98.91
124	3	0.23	1277	99.15
127	3	0.23	1280	99.38
129	3	0.23	1283	99.61
132	2	0.16	1285	99.77
135	1	0.08	1286	99.84
141	1	0.08	1287	99.92
144	1	0.08	1288	100.00

Frequency Missing = 30

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Distribution of Bayley II Scores
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: IFMDI (MDI)

Moments			
N	1954	Sum Weights	1954
Mean	77.9662231	Sum Observations	152346
Std Deviation	18.2394857	Variance	332.678838
Skewness	0.04888953	Kurtosis	-0.5940593
Uncorrected SS	12527564	Corrected SS	649721.771
Coeff Variation	23.3940865	Std Error Mean	0.41262003

Basic Statistical Measures			
Location		Variability	
Mean	77.96622	Std Deviation	18.23949
Median	80.00000	Variance	332.67884
Mode	49.00000	Range	88.00000
		Interquartile Range	28.00000

Tests for Location: Mu0=0				
Test		Statistic	p Value	
Student's t	t	188.954	Pr > |t|	<.0001
Sign	M	977	Pr >= |M|	<.0001
Signed Rank	S	955017.5	Pr >= |S|	<.0001

Quantiles (Definition 5)	
Quantile	Estimate
100% Max	137
99%	122
95%	107
90%	101
75% Q3	91
50% Median	80
25% Q1	63
10%	49
5%	49
1%	49
0% Min	49

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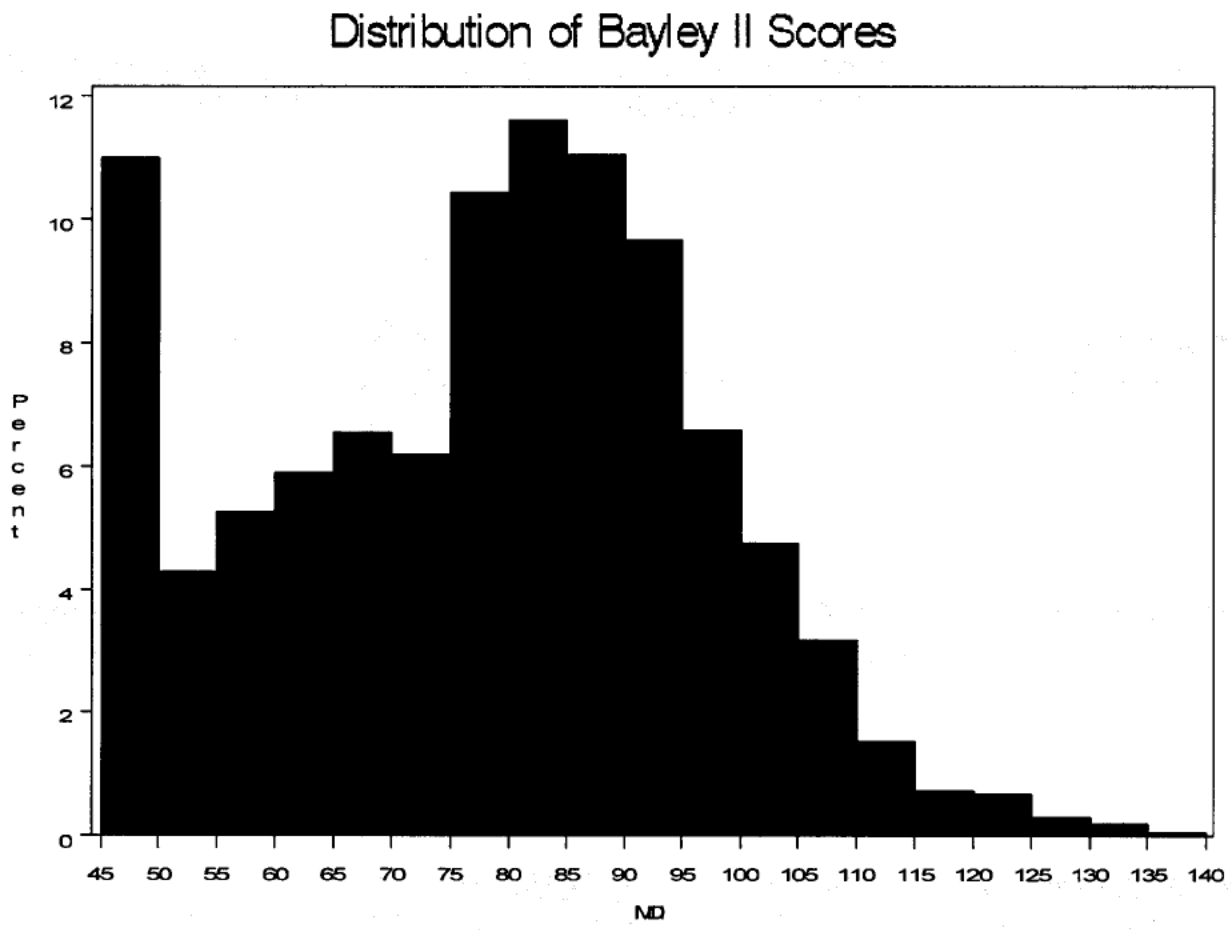
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: IFMDI (MDI)

Extreme Observations			
Lowest		Highest	
Value	Obs	Value	Obs
49	17581	130	13545
49	17576	130	14333
49	17480	130	15194
49	17464	132	14411
49	17417	137	16058

Missing Values			
		Percent Of	
Missing Value	Count	All Obs	Missing Obs
.	9	0.46	100.00



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Distribution of Bayley II Scores (GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: IFPDI (PDI)

Moments			
N	1936	Sum Weights	1936
Mean	82.2716942	Sum Observations	159278
Std Deviation	18.9707934	Variance	359.891002
Skewness	-0.4054748	Kurtosis	-0.6949182
Uncorrected SS	13800460	Corrected SS	696389.089
Coeff Variation	23.0587124	Std Error Mean	0.4311544

Basic Statistical Measures			
Location		Variability	
Mean	82.27169	Std Deviation	18.97079
Median	86.00000	Variance	359.89100
Mode	49.00000	Range	83.00000
		Interquartile Range	25.00000

Tests for Location: Mu0=0				
Test		Statistic		p Value
Student's t	t	190.8172	Pr > |t|	<.0001
Sign	M	968	Pr >= |M|	<.0001
Signed Rank	S	937508	Pr >= |S|	<.0001

Quantiles (Definition 5)	
Quantile	Estimate
100% Max	132
99%	119
95%	109
90%	104
75% Q3	95
50% Median	86
25% Q1	70
10%	49
5%	49
1%	49
0% Min	49

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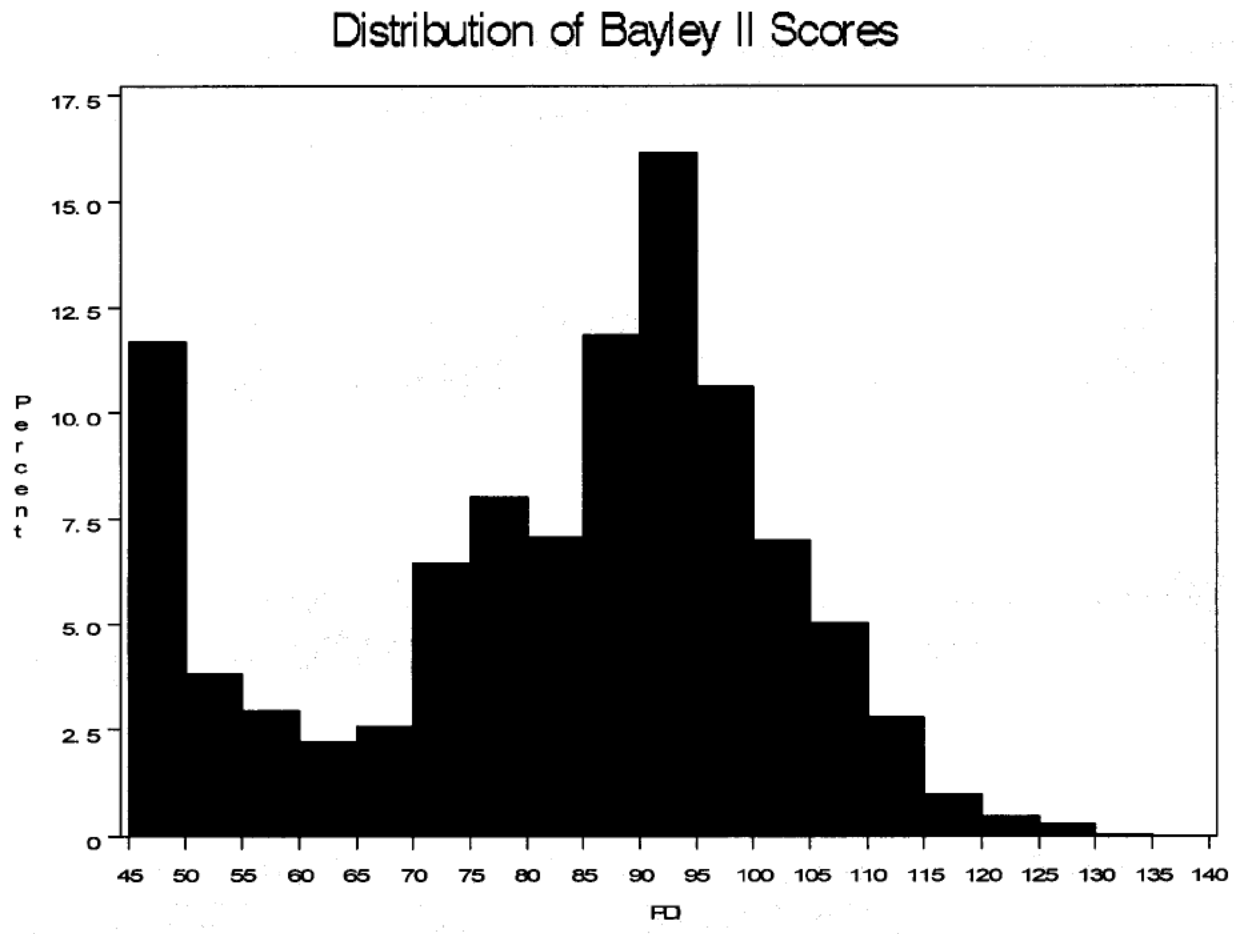
The UNIVARIATE Procedure
Variable: IFPDI (PDI)

Extreme Observations			
Lowest		Highest	
Value	Obs	Value	Obs
49	17612	125	16924
49	17581	125	17189
49	17576	128	14463
49	17563	128	15817
49	17554	132	14387

Missing Values			
		Percent Of	
Missing Value	Count	All Obs	Missing Obs
.	27	1.38	100.00



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Distribution of Bayley III Scores
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: NF9ABSCC (Cognitive Composite)

Moments			
N	1314	Sum Weights	1314
Mean	89.8500761	Sum Observations	118063
Std Deviation	15.0655199	Variance	226.96989
Skewness	-0.2595197	Kurtosis	0.29365934
Uncorrected SS	10905981	Corrected SS	298011.465
Coeff Variation	16.767398	Std Error Mean	0.41561043

Basic Statistical Measures			
Location		Variability	
Mean	89.85008	Std Deviation	15.06552
Median	90.00000	Variance	226.96989
Mode	90.00000	Range	86.00000
		Interquartile Range	20.00000

Tests for Location: Mu0=0				
Test	Statistic		p Value	
Student's t	t	216.1882	Pr > |t|	<.0001
Sign	M	657	Pr >= |M|	<.0001
Signed Rank	S	431977.5	Pr >= |S|	<.0001

Quantiles (Definition 5)	
Quantile	Estimate
100% Max	140
99%	125
95%	115
90%	110
75% Q3	100
50% Median	90
25% Q1	80
10%	70
5%	60
1%	54
0% Min	54

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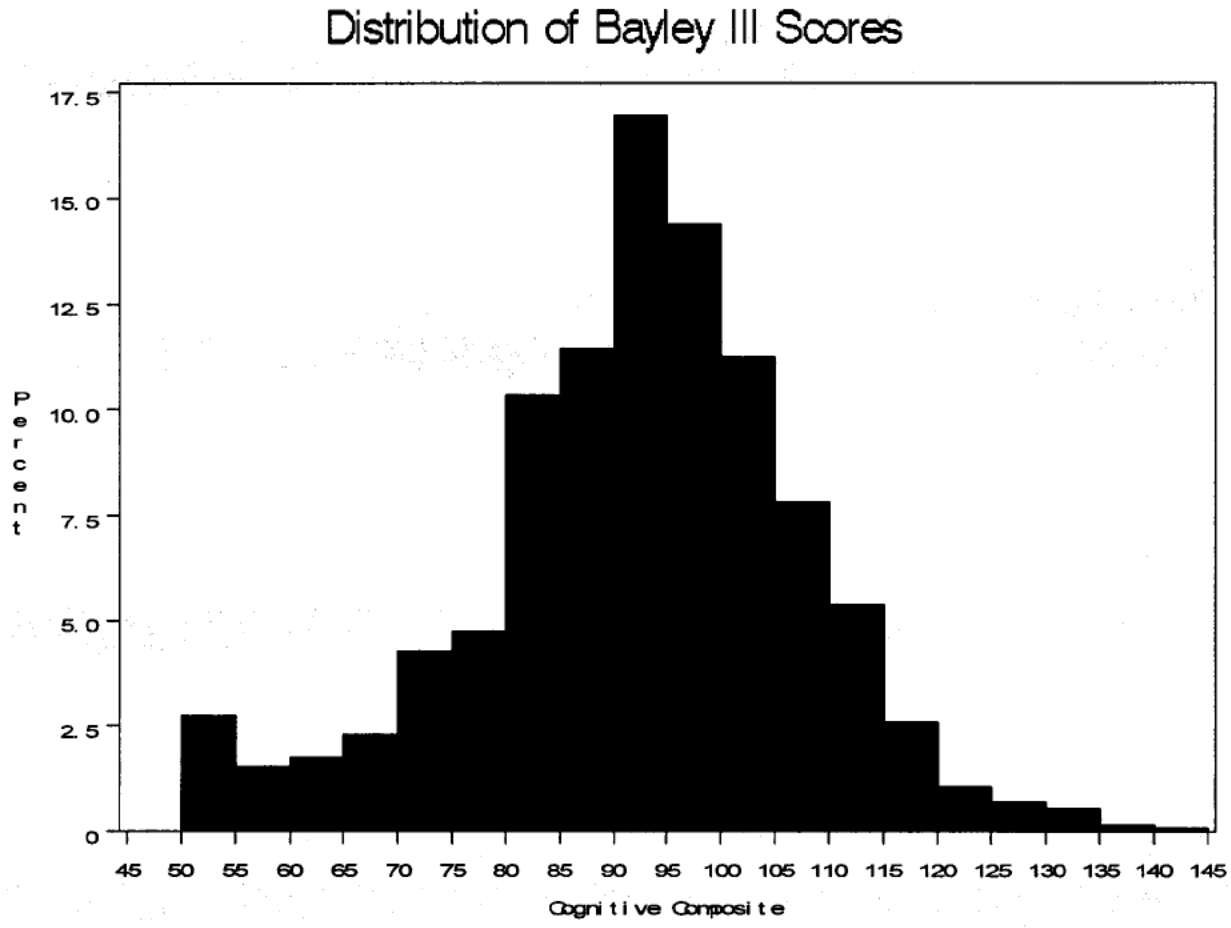
The UNIVARIATE Procedure
Variable: NF9ABSCC (Cognitive Composite)

Extreme Observations			
Lowest		Highest	
Value	Obs	Value	Obs
54	17819	130	16684
54	17736	130	17531
54	17400	135	17287
54	17324	135	18047
54	17010	140	16696

Missing Values			
Missing Value	Count	Percent of All Obs	Percent of Missing Obs
.	4	0.30	100.00



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Distribution of Bayley III Scores
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: NF9ABSLC (Language Composite)

Moments			
N	1288	Sum Weights	1288
Mean	84.673913	Sum Observations	109060
Std Deviation	17.1522513	Variance	294.199723
Skewness	-0.1139674	Kurtosis	0.0424927
Uncorrected SS	9613172	Corrected SS	378635.043
Coeff Variation	20.2568307	Std Error Mean	0.4779288

Basic Statistical Measures			
Location		Variability	
Mean	84.67391	Std Deviation	17.15225
Median	86.00000	Variance	294.19972
Mode	91.00000	Range	98.00000
		Interquartile Range	23.00000

Tests for Location: Mu0=0				
Test	Statistic		p Value	
Student's t	t	177.1685	Pr > |t|	<.0001
Sign	M	644	Pr >= |M|	<.0001
Signed Rank	S	415058	Pr >= |S|	<.0001

Quantiles (Definition 5)	
Quantile	Estimate
100% Max	144
99%	124
95%	112
90%	106
75% Q3	97
50% Median	86
25% Q1	74
10%	62
5%	50
1%	46
0% Min	46

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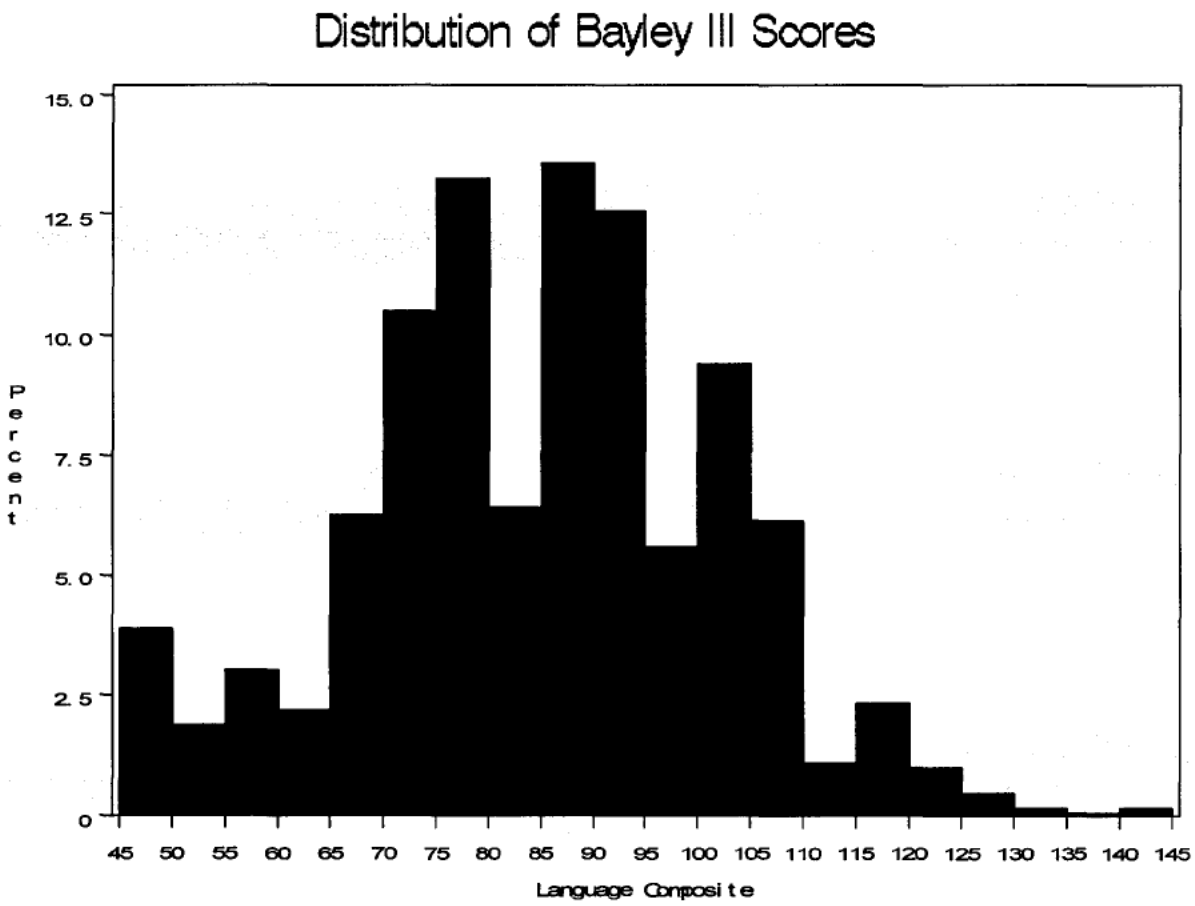
The UNIVARIATE Procedure
Variable: NF9ABSLC (Language Composite)

Extreme Observations			
Lowest		Highest	
Value	Obs	Value	Obs
46	17819	132	15838
46	17736	132	17798
46	17400	135	17824
46	17324	141	15824
46	17010	144	15879

Missing Values			
Missing Value	Count	Percent Of All Obs	Percent Of Missing Obs
.	28	2.12	93.33
P	2	0.15	6.67
Total	30	2.28	100.00



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Distribution of Bayley III Scores
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: coglang (Bayley III Cognitive Composite + Language Composite)

Moments			
N	1284	Sum Weights	1284
Mean	174.629283	Sum Observations	224224
Std Deviation	29.716241	Variance	883.05498
Skewness	-0.2777984	Kurtosis	0.39471901
Uncorrected SS	40289036	Corrected SS	1132959.54
Coeff Variation	17.0167571	Std Error Mean	0.82929942

Basic Statistical Measures			
Location		Variability	
Mean	174.6293	Std Deviation	29.71624
Median	176.0000	Variance	883.05498
Mode	169.0000	Range	171.00000
		Interquartile Range	36.00000

Tests for Location: Mu0=0				
Test		Statistic	p Value	
Student's t	t	210.5745	Pr > |t|	<.0001
Sign	M	642	Pr >= |M|	<.0001
Signed Rank	S	412485	Pr >= |S|	<.0001

Quantiles (Definition 5)	
Quantile	Estimate
100% Max	271
99%	240
95%	221
90%	211
75% Q3	193
50% Median	176
25% Q1	157
10%	137
5%	118
1%	100
0% Min	100

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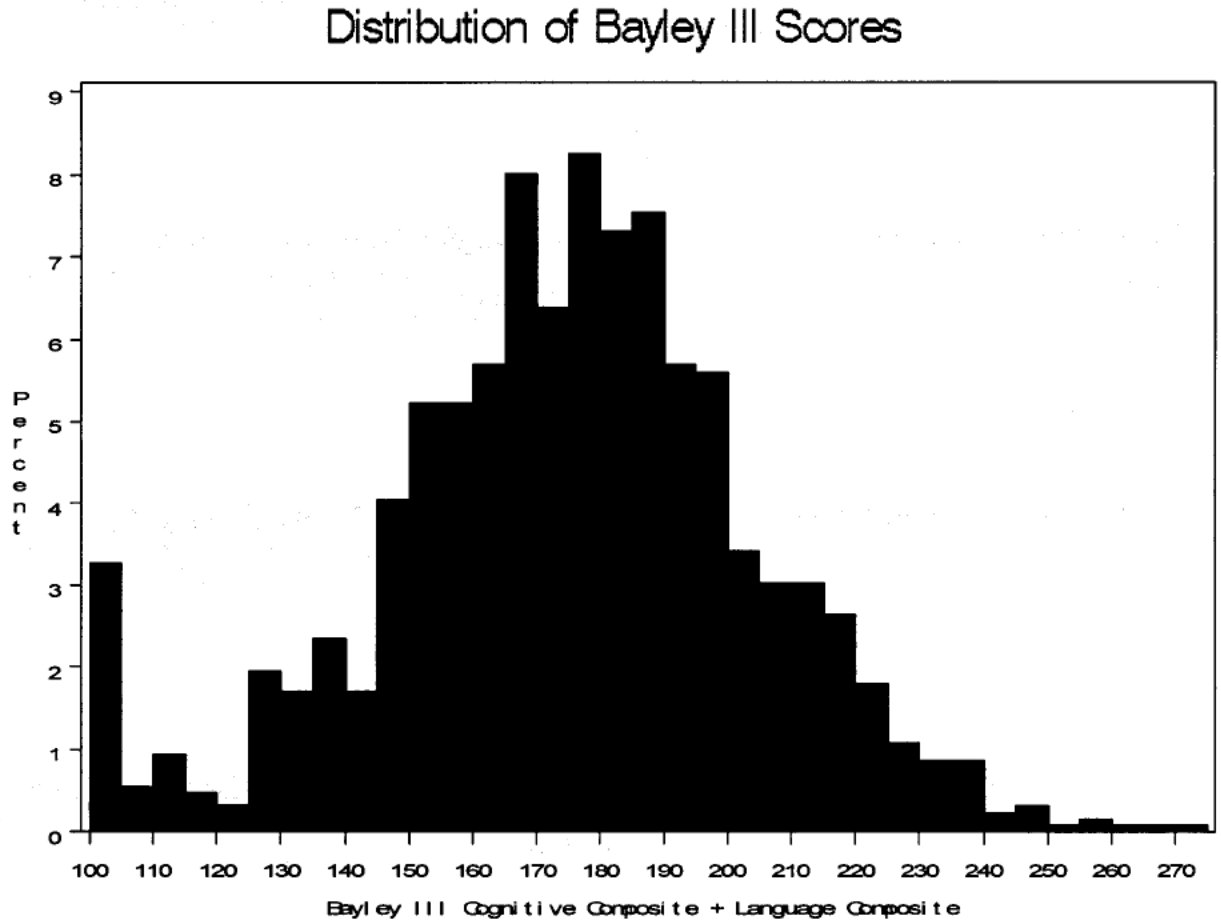
Distribution of Bayley III Scores
(GDB infants born 2005-2007)

The UNIVARIATE Procedure
Variable: coglang (Bayley III Cognitive Composite + Language Composite)

Extreme Observations			
Lowest		Highest	
Value	Obs	Value	Obs
100	17819	257	17531
100	17736	259	15879
100	17400	264	18047
100	17324	269	16696
100	17010	271	15824

Missing Values			
		Percent Of	
Missing Value	Count	All Obs	Missing Obs
.	34	2.58	100.00



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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Vohr, Betty; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP
Date: Tuesday, June 02, 2009 11:48:50 AM

Correction: it is true that all of the windows OPEN by the end of 2010, but the last window will close in April 2011.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 10:17 AM
To: Gantz, Marie; Vaucher, Yvonne; Vohr, Betty; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

SO all the windows are complete by the end of 2010, correct??
Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, May 27, 2009 7:44 PM
To: Vaucher, Yvonne; Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

Attached is a breakdown by month of when SUPPORT FU windows will be opening in 2009 through the rest of the study (for kids yet to have FU).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, May 26, 2009 3:56 PM
To: Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

I agree with Betty that we should in clude the motor scales of the Bayley 3 from some point onwards for all study follow-up visits. Abhik, what proportion of the

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Support sample will have the Bayley 3 including motor scales vs the abbreviated Bayley 3 if we began to use the complete Bayley by September 1, October 1, November 1 allowing ~3 months for the additional certification?

Let's talk about this at the next follow-up call. Should we move the call up to June since the sooner we make a decision, the sooner we will complete moptor scales certification and be able to begin using the data? If most centers are already doing the motor scales the certification should be fairly rapid.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Tuesday, May 26, 2009 10:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

Good idea. I have also brought up previously perfoming the entire Bayley III including fine and gross motor going forward. Test time has decreased. Most sites are already doing the motor component. We would need to certify testers on the motor scores and have Abik give us a start-up time. Both Terri Leach and Vicki Watson at our site support this addition.
Betty

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 26, 2009 9:57 AM
To: Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

Yvonne
Marie Gantz is the statistician for SUPPORT. The sample size for SUPPORT was determined based on the primary outcomes of BPD/ROP/ and death. FU was originally listed as a secondary outcome.

Confidentially, children are scoring better on the Bayley III as opposed to the Bayley II. For an upcoming trial, we are using a cognitive score of < 85 on the Bayley III as one component of neurodevelopmental impairment.

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Perhaps we should discuss this one the follow up call scheduled for mid-July?
let me know

Regards
Rose

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 22, 2009 3:08 PM
To: Betty_Vohr@brown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support FUP

Betty and Rose,

As I have not been part of the primary group, who is the best person(s) to talk to at RTI and within our follow-up group about the sample size/Bayley 3 questions for the Support trial so I can best understand the issues?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Vohr, Betty; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP
Date: Tuesday, June 02, 2009 11:45:52 AM

Yes, that is correct.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 10:17 AM
To: Gantz, Marie; Vaucher, Yvonne; Vohr, Betty; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

SO all the windows are complete by the end of 2010, correct??
Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, May 27, 2009 7:44 PM
To: Vaucher, Yvonne; Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

Attached is a breakdown by month of when SUPPORT FU windows will be opening in 2009 through the rest of the study (for kids yet to have FU).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, May 26, 2009 3:56 PM
To: Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

I agree with Betty that we should in clude the motor scales of the Bayley 3 from some point onwards for all study follow-up visits. Abhik, what proportion of the

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Support sample will have the Bayley 3 including motor scales vs the abbreviated Bayley 3 if we began to use the complete Bayley by September 1, October 1, November 1 allowing ~3 months for the additional certification?

Let's talk about this at the next follow-up call. Should we move the call up to June since the sooner we make a decision, the sooner we will complete moptor scales certification and be able to begin using the data? If most centers are already doing the motor scales the certification should be fairly rapid.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Tuesday, May 26, 2009 10:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

Good idea. I have also brought up previously perfoming the entire Bayley III including fine and gross motor going forward. Test time has decreased. Most sites are already doing the motor component. We would need to certify testers on the motor scores and have Abik give us a start-up time. Both Terri Leach and Vicki Watson at our site support this addition.
Betty

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 26, 2009 9:57 AM
To: Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

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Perhaps we should discuss this one the follow up call scheduled for mid-July?
let me know

Regards
Rose

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 22, 2009 3:08 PM
To: Betty_Vohr@brown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support FUP

Betty and Rose,

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Thanks.

Yvonne

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Roy Heyne
Subject: Re: SUPPORT 6-7 year FU
Date: Saturday, May 30, 2009 4:27:29 PM
Attachments: Comments regarding 6to7yoneurofu.doc

Rose--comments from our center--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 5/8/09 8:16 AM >>>
Hi,

Attached is the grid of the SUPPORT 6-7 year visit. Please review with your follow up staff and send suggestions by May 29. The protocol is in the final stage of revision and input must be received by May 29. If we do not hear from you, we will assume you have no further suggestions.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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Comments regarding 6-7 year SUPPORT Neuroimaging and Neurodevelopmental Outcomes
Dallas 5/29/09

Have discussed this with our psychologist, and in general we think the proposed set of assessments and parent questionnaires constitute a very good battery of assessment tools.

That said, we think it will be important to further delineate how the results of these assessments will be used in evaluating and interpreting outcomes, especially with regards to tools which are intended for screening purposes, such as the SCQ. We need to be cautious about interpreting results of a screening tool with limited specificity and positive predictive value as diagnostic of ASD.

Moreover, the intended use of an ASD screening tool in analysis and interpretation of outcomes would also be one important factor to consider in choosing one tool over another. The SCQ does have fairly sensitivity in multiple studies assessing its validity, though design of these studies do vary and sample sizes tend to be relatively small. However, specificity is as low as 58% in some studies. Of course, both parameters depend on what cutoff is used; and a paper by Allen et al (J Autism Dev Disord 37:1272-1278 from 2007) suggests that a lower cut-off has a better AUC on ROC analysis than the standard one. Several authors make the point that this tool should not be used for diagnostic purposes.

According to the information provided by Myriam, the SRS may a lower sensitivity but higher specificity. Again, depending on the intended use of results, the additional information regarding different dimensions may or may not be of additional value, especially considering this is still a screening tool.

Finally, on a totally different note, our psychologist thinks the time estimates for some of the psych tests may be somewhat optimistic. As stated, the neuro + psych evals add up to about 2.5 hours and the questionnaires to about 1.5 hours. Depending on the child and the parent, these may need to be administered sequentially, rather than in parallel. That would add up to a 4 hour session, not including breaks, which is long, but not unusual for a thorough psychological evaluation. Our psychologist indicated it would be important to have good testing finesse in being able to offer min-breaks in-between various tests, and think that a 6-7 year old is likely to require more than 1 break.

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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for SUPPORT forms
Date: Friday, May 29, 2009 12:01:00 AM

---

yes

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

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From: Vohr, Betty
To: Vaucher, Yvonne
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support FUP
Date: Friday, May 29, 2009 11:10:16 PM

Yvonne,
I dont see a disadvantage. It would not be used specifically for the outcome analysis of the Support sample, but certainly could be used for other studies or for the comparison of Bayley III to II. As it is several of the sites are already doing it but not entering the data.
Betty

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Friday, May 29, 2009 9:34 PM
To: Vohr, Betty
Subject: RE: Support FUP

Betty,

Is there a disadvantage of doing the whole Bayley on the remaining Support sample? We don't have to use it in our final analysis, but it may give us more information about what to do with the Bayley III in future studies and how to compare the Bayley II and III, especially as we would have done the abbreviated and full Bayley within the same group. ¼ of the Support population would be 300+ children .

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Friday, May 29, 2009 5:41 PM
To: Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

That would mean it could not be used for Support. However, I do believe the sooner we start the motor scales the better.
(b) (6) [redacted]
BV

From: Gantz, Marie [mgantz@rti.org]
Sent: Friday, May 29, 2009 2:05 PM
To: Vaucher, Yvonne; Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

I am out of town until Tuesday, but I will respond to your emails when I return.

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Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, May 28, 2009 10:33 AM
To: Gantz, Marie; Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP

Marie,

So if we started to do a full Bayley in 9/09 we would have the full Bayley on ~ ¼ of our sample?

Yvonne

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Cc: Das, Abhik; Gantz, Marie; Finer, Neil

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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline; Gantz, Marie
Subject: RE: SUPPORT
Date: Friday, May 29, 2009 12:21:29 PM

Hi. See below-thank you

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 22, 2009 8:57 AM
To: Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn; Hamer, Faithe Angeline
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported--F/U visit June 23rd
CENTER	NETWORK	BPD_message
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.-NG07 almost complete-will be entered
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.-NG07 almost complete- will be entered
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Completed and ready to enter
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.-Still in hospital
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.- Still in hospital
CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.--Visit on May 13th-waiting on return of Bayley info from examiner-you can expect soon
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.--- Visit on May 13th-waiting on return of Bayley info from examiner-you can expect soon

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for SUPPORT forms
Date: Thursday, May 28, 2009 1:54:54 PM

Yes-ok-even with subsequent explanation-pablo
-----Original Message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: Oh William (E-mail) <william_oh@brown.edu>
To: Ed Donovan <edward.donovan@cchmc.org>
To: <kurt.schibler@cchmc.org>
To: <Bradley.yoder@hsc.utah.edu>
To: Roger Faix <Roger.Faix@hsc.utah.edu>
To: Brenda Poindexter <bpoindex@iupui.edu>
To: Krisa VanMeurs <vanmeurs@leland.stanford.edu>
Cc: Stephanie (NIH/NICHD) [E] Archer <archerst@mail.nih.gov>
To: <cotte010@mc.duke.edu>
To: Ronald GOldberg <goldb008@mc.duke.edu>
To: Seetha Shankaran <sshankar@med.wayne.edu>
To: MIckey Caplan <mca113@Northwestern.edu>
To: Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>
To: Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>
To: <aaf2@po.cwru.edu>
To: Michelle Walsh <mcw3@po.cwru.edu>
To: Abhik Das <adas@rti.org>
To: Dennis Wallace <dwallace@rti.org>
Cc: <kzaterka@rti.org>
Cc: Meg Cunningham <mcunningham@rti.org>
To: Poole Kenneth (E-mail) <poo@rti.org>
To: Kristi Watterberg <kwatterberg@salud.unm.edu>
To: Stevenson David (E-mail) <dstevenson@stanford.edu>
To: <ifrantz@tuftsmedicalcenter.org>
To: <ambal@uab.edu>
Cc: Neil Finer <nfiner@ucsd.edu>
Cc: Wade Rich <wrich@ucsd.edu>
To: Ed Bell <Edward-bell@uiowa.edu>
To: <rohls@unm.edu>
To: Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>
To: Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>
To: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>

Sent: 5/28/2009 10:07:49 AM
Subject: Request for SUPPORT forms

Hi

Dr. Finer has requested permission to use the SUPPORT forms and manual for his R34 clinical trial planning grant for the PreSox trial sponsored by NICHD. Please send me a yes/no vote by June 2.

Thanks
Rose

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Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for SUPPORT forms
Date: Thursday, May 28, 2009 12:27:33 PM

Rose,

I vote yes, if it is appropriate for me to vote.

David

> Hi
>
> Dr. Finer has requested permission to use the SUPPORT forms and manual for his R34 clinical trial planning grant for the PreSox trial sponsored by NICHD. Please send me a yes/no vote by June 2.
>
> Thanks
> Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:44:09 PM

Yes.
Krisa

>Hi
>Dr. Finer has requested permission to use the SUPPORT forms and
>manual for his R34 clinical trial planning grant for the PreSox
>trial sponsored by NICHD. Please send me a yes/no vote by June 2.
>
>Thanks
>Rose
>
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
>Eunice Kennedy Shriver National Institute of Child Health and Human
>Development
>National Institutesof Health
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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:40:31 AM

yes, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 11:08 AM
To: Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; Cunningham, Meg; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:20:46 AM

---

yes

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 11:08 AM
To: Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; Cunningham, Meg; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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From: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:15:46 AM

YES (love these easy questions!)
Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 11:08 AM
To: Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Poindexter, Brenda B; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; Cunningham, Meg; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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Rosemary D. Higgins, MD
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Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:14:27 AM

Yes.
Richard

Higgins, Rosemary (NIH/NICHD) [E] wrote:
>
> Hi
>
> Dr. Finer has requested permission to use the SUPPORT forms and manual
> for his R34 clinical trial planning grant for the PreSox trial
> sponsored by NICHD. Please send me a yes/no vote by June 2.
>
>
>
> Thanks
> Rose
>
>
>
> Rosemary D. Higgins, MD
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
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> Center for Developmental Biology and Perinatal Medicine
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> higginsr@mail.nih.gov
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>
>

--
Richard A. Ehrenkranz, MD

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fax: 203-688-5426

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:09:38 AM

Yes

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 10:08 AM
To: Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; Cunningham, Meg; Finer, Neil; Rich, Wade
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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for SUPPORT forms
Date: Thursday, May 28, 2009 11:08:41 AM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 28, 2009 11:08 AM
To: Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Wallace, Dennis; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole, W. Kenneth; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Finer, Neil; Rich, Wade
Subject: Request for SUPPORT forms

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From: Gantz, Marie
To: Vaucher, Yvonne; Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Finer, Neil
Subject: RE: Support FUP
Date: Wednesday, May 27, 2009 7:44:06 PM
Attachments: SUPPORT FU windows by month 5-27-09.rtf

Attached is a breakdown by month of when SUPPORT FU windows will be opening in 2009 through the rest of the study (for kids yet to have FU).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, May 26, 2009 3:56 PM
To: Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

I agree with Betty that we should in clude the motor scales of the Bayley 3 from some point onwards for all study follow-up visits. Abhik, what proportion of the Support sample will have the Bayley 3 including motor scales vs the abbreviated Bayley 3 if we began to use the complete Bayley by September 1, October 1, November 1 allowing ~3 months for the additional certification?

Let's talk about this at the next follow-up call. Should we move the call up to June since the sooner we make a decision, the sooner we will complete moptor scales certification and be able to begin using the data? If most centers are already doing the motor scales the certification should be fairly rapid.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Tuesday, May 26, 2009 10:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil

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Subject: RE: Support FUP

Good idea. I have also brought up previously perfoming the entire Bayley III including fine and gross motor going forward. Test time has decreased. Most sites are already doing the motor component. We would need to certify testers on the motor scores and have Abik give us a start-up time. Both Terri Leach and Vicki Watson at our site support this addition.
Betty

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 26, 2009 9:57 AM
To: Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

Yvonne
Marie Gantz is the statistician for SUPPORT. The sample size for SUPPORT was determined based on the primary outcomes of BPD/ROP/ and death. FU was originally listed as a secondary outcome.

Confidentially, children are scoring better on the Bayley III as opposed to the Bayley II. For an upcoming trial, we are using a cognitive score of < 85 on the Bayley III as one component of neurodevelopmental impairment.

Perhaps we should discuss this one the follow up call scheduled for mid-July?
let me know

Regards
Rose

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 22, 2009 3:08 PM
To: Betty_Vohr@brown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support FUP

Betty and Rose,

As I have not been part of the primary group, who is the best person(s) to talk to at RTI and within our follow-up group about the sample size/Bayley 3 questions for the Support trial so I can best understand the issues?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.

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Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

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Month FU windows open for SUPPORT infants yet to have 18 month FU

The FREQ Procedure

Table of fumonth by fuyear

fumonth(Month FU opens)	fuyear(Year FU opens)		
Frequency	2009	2010	Total
1	7	40	47
2	10	20	30
3	11	31	42
4	14	22	36
5	31	25	56
6	26	19	45
7	20	16	36
8	29	25	54
9	16	20	36
10	36	21	57
11	21	26	47
12	30	2	32
Total	251	267	518

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From: Susan Hintz
To: Kris Zaterka
Cc: adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Krisa Van Meurs
Subject: supplemental SUPPORT MRI white matter summary classification form
Date: Tuesday, May 26, 2009 5:59:28 PM
Attachments: SUPPORT_MRI_Supplemental.docx

Hi all,

Attached is the supplemental SUPPORT MRI white matter injury summary classification form. Kris, I know this is probably coming out of left field for you. Rose and Abhik and I discussed it in a few emails when I was trying to get an idea of whether we really could or should do this.

Here is the issue in a nutshell: There have been an increasing number of papers reporting more than one MRI reader to establish reliability/agreement - and this was particularly evident at the recent PAS. Also, we have 2 central readers for the CUS. So, it is now becoming painfully clear that we need to have at least a SAMPLE of the 500 MRI's read by another neuroradiologist. Abhik and Rose and I have discussed using a streamlined summary classification form rather than trying to have the 2nd reader go through ALL of the very detailed MRI central reader form. Thus, our "main" central reader Dr. Barnes would fill out this supplemental form and the central reader from, while the 2nd central reader would only fill this form - we could ascertain concordance using this supplemental form.

Based on some calculations that Abhik did for me, we would probably need the 2nd reader to read 80-100 randomly selected MRI's to establish agreement.

So - long story - this attached is the supplemental form, already "OK'd" by Dr. Barnes. I am gathering some names of potential 2nd central readers (I have gotten a couple names already from Dr. Slovis, I have asked Dr. Barnes, and I will ask one other person I know in UCSF for names).

Kris - can you make this into a "real" form? However you magically do that... Abhik and Kris - note that in A.2, I indicate that the ACTUAL SCORE (numerical) should be entered in the box. This won't be a problem from the perspective of data entry, correct?

Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304

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fax: 650-725-8351

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A. SUMMARY CLASSIFICATIONS: WHITE MATTER INJURY IN PRETERM INFANTS

A.1 Miller Classifications; Check one box for each hemisphere	Normal	Minimal	Moderate	Severe	Not interpretable
Right					
Left					

KEY: Miller Classifications (ref 1-3)	NOTE per Miller, et. al. (UCSF group) **WM abnormalities included foci of abnormal T1 hyperintensity in the absence of marked T2 hypointensity in the periventricular area. The constellation of T1 hyperintensity in the absence of T2 hypointensity most likely represented areas of gliosis. Areas of cavitation also included**
Normal	No WM lesions
Minimal	3 or fewer areas of T1 signal abnormality measuring <2 mm
Moderate	3 or more areas of T1 signal abnormality or these areas measuring < 2 mm but >5% of hemisphere involved
Severe	>5% of hemisphere involved

A.2 Inder Classifications; Enter score in appropriate box for each hemisphere	Normal (5-6)	Mild (7-9)	Moderate (10-12)	Severe (13-15)	Not interpretable
Right					
Left					

Key: Inder Classifications (ref 4-6)	**Score = 1**	**Score =2**	**Score =3**
1) WM signal abnormalities (on axial imaging)	Normal T1 and T2 throughout	Focal regions of high T1 or T2 signal (2 or fewer regions per hemisphere)	Multiple regions of high T1 or T2 signal (> 2 regions per hemisphere)
2) Perventricular WM volume loss (axial and sagittal) – looking at ratio of periventric WM to vent volume	Normal PV WM volume	Mild reduction in WM volume with mild-mod vent size increase	Marked reduction in WM volume often with marked increase in size of vent or extra-ax space
3) Cystic abnormalities	Normal	< 2 mm single focal cyst	Multiple cysts or a single large (>2 mm) focal cyst
4) Ventricular dilatation (axial and sagittal)	Normal with no vent dilation	Mod enlargement resulting in mild rounding of front horns, minimal enlargement of temporal horns and mod enlarge of occipital horns	Global enlargement of a moderate to severe nature
5) Thinning of the CC (sagittal and coronal T1)	Normal, thick CC	Focal thinning of the CC often visible in mid region of CC	Global thinning

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References:

1) Miller SP, et. al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. AJNR 2003; 24:1661-9
2) Miller SP, et. al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Peds 2005; 147:609-616
3) Glass H, et. al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics 2008; 122:299-305
4) Inder TE, et. al. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. J Pediatr 2003; 143:171-179
5) Woodward LJ, et. al. Can neurobehavioural examination predict the presence of cerebral injury in the very low birth weight infant? J Dev Behav Pediatr 2004; 25:326-334
6) Woodward LJ, et. al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. NEJM 2006; 355:685-694

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From: Vohr, Betty
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Gantz, Marie; Finer, Neil
Subject: RE: Support FUP
Date: Tuesday, May 26, 2009 1:30:10 PM

Thanks Abik

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, May 26, 2009 10:05 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

The sample size calculations in the SUPPORT protocol also mention the follow up outcome of death or NDI, though the primary outcomes are death or BPD and death or ROP. (Page 24 of the protocol states: "Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome.") Of course, these were based on the Bayley II and may not obtain for the Bayley III. I am happy to discuss this issue as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 26, 2009 9:57 AM
To: Vaucher, Yvonne; Betty_Vohr@brown.edu
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support FUP

Yvonne
Marie Gantz is the statistician for SUPPORT. The sample size for SUPPORT was determined based on the primary outcomes of BPD/ROP/ and death. FU was originally listed as a secondary outcome.

Confidentially, children are scoring better on the Bayley III as opposed to the Bayley II. For an upcoming trial, we are using a cognitive score of < 85 on the Bayley III as one component of neurodevelopmental impairment.

Perhaps we should discuss this one the follow up call scheduled for mid-July?
let me know

Regards
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, May 22, 2009 3:08 PM
To: Betty_Vohr@brown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support FUP

Betty and Rose,

As I have not been part of the primary group, who is the best person(s) to talk to at RTI and within our follow-up group about the sample size/Bayley 3 questions for the Support trial so I can best understand the issues?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

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From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Evans, Patricia W
Subject: RE: SUPPORT
Date: Tuesday, May 26, 2009 10:48:12 AM

For the follow-up portion, baby (b) (6) will hopefully be scheduled within a month. Mom and I are currently coordinating a time that is good for her to come in.

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713.500.6813 (office)
713.500.5794 (fax)
713.760(b) (6) (pager)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Evans, Patricia W
Sent: Friday, May 22, 2009 1:44 PM
To: Poundstone, Margaret
Subject: FW: SUPPORT
Importance: High

Present for you!

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, May 22, 2009 8:02 AM
To: Kennedy, Kathleen A; Tyson, Jon E; Mcdavid, Georgia E; Evans, Patricia W
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20892
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Julie Rohr
Subject: Re: SUPPORT
Date: Friday, May 22, 2009 2:33:47 PM

Hi Rose,
This little one is still hospitalized and will hopefully be discharged (b) (6) At status the NG03 and NG07 will be entered along with the entire SUPPORT chart.
At 36 weeks she was intubated and on conventional ventilation post PDA ligation. Unfortunately it took her a week to extubate to Hudson CPAP.
If things continue to go well for her, I think her info will be entered by the end of the month.
Have a great Memorial Day.
Julie

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 5/22/2009 7:07 AM >>>
Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	BPD_message
26	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; mcollins@peds.uab.edu; scosby@peds.uab.edu; vphillips@peds.uab.edu
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Friday, May 22, 2009 10:34:03 AM

Rose.

We will work on it.

Wally

-----Original Message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "mcollins@peds.uab.edu" <mcollins@peds.uab.edu>; "scosby@peds.uab.edu" <scosby@peds.uab.edu>; "vphillips@peds.uab.edu" <vphillips@peds.uab.edu>
Cc: "Gantz, Marie" <mgantz@rti.org>
Sent: 5/22/2009 8:01 AM
Subject: SUPPORT

Hi,

We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

THIS IS MAGNIFICENT GIVEN YOUR OUTSTANDING RECRUITMENT!!!

Thanks for all the hard work!!
Rose

CENTER

NETWORK

ROP_message

16

(b) (6)

SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

16

(b) (6)

SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

16

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(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

16

(b) (6)

Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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higginsr@mail.nih.gov

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From: Hensman, Angelita
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Laptook, Abbot; Vohr, Betty; Ventura, Suzy
Subject: RE: SUPPORT
Date: Friday, May 22, 2009 10:31:21 AM

See answers below in blue.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 22, 2009 9:00 AM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Ventura, Suzy
Cc: Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

THIS IS EXCEPTIONAL GIVEN YOUR OUTSTANDING RECRUITMENT!!!

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
14	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Not due in follow up till (b) (6)
CENTER	NETWORK	BPD_message
14	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Will be entered with NG03 and NG07 at status.
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; "nancy newman"
Cc: "Gantz, Marie"
Subject: RE: SUPPORT
Date: Friday, May 22, 2009 10:03:33 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 22, 2009 8:51 AM
To: mcw3@cwru.edu; Bonnie Siner; nancy newman
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

THIS IS SPECTACULAR GIVEN YOUR HIGH RECRUITMENT!!!

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	Appt. scheduled for 5/28/09
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
		No show for appt. 5/21/09 – trying to reschedule

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Thursday, May 21, 2009 5:59:56 PM
Attachments: Infants with missing outcomes 05-21-09.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this week.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

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From: Zaterka-Baxter, Kristin
To: ahensman@wihri.org; Archer, Stephanie (NIH/NICHD) [E]; Bethany Ball; BMackinnon@tuftsmedicalcenter.org; Conra Lacy; Cunningham, Meg; ellen_hale@oz.ped.emory.edu; Faithe Hammer; Georgia.E.McDavid@uth.tmc.edu; grisbyca@email.uc.edu; Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Johnson, Karen; karen.osborne@hsc.utah.edu; ldw@iupui.edu; mcollins@peds.uab.edu; melissa.leps@utsouthwestern.edu; monica.konstantino@yale.edu; nancy newman; Nancy.Miller@UTSouthwestern.edu; Newman, Jamie; rbara@med.wayne.edu; Michelle Tidwell; Shirley Cosby; Poundstone, Margaret ; Kimberley A Fisher; Everett-Thomas, Ruth; Rich, Wade; npeters@wfubmc.edu; Reubens, Linda
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Subject: RE: Support Trial Oximeter Returns
Date: Thursday, May 21, 2009 3:42:47 PM
Attachments: SUPPORTCoordinators_Updated20090303.doc
SUPPORT Oximeter by Center Home 20080131.pdf

Dear all,

Just a reminder to let me know when you have received all your original oximeters from other centers so that we can coordinate a convenient time for the Massimo rep to come to your site to convert your oximeters.
Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Tuesday, March 03, 2009 5:33 PM
To: 'ahensman@wihri.org'; 'Archer, Stephanie (NIH/NICHD) [E]'; Bethany Ball; 'BMackinnon@tuftsmedicalcenter.org'; 'Conra Lacy'; Cunningham, Meg; 'ellen_hale@oz.ped.emory.edu'; 'Faithe Hammer'; 'Georgia.E.McDavid@uth.tmc.edu'; 'grisbyca@email.uc.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Huitema, Carolyn Petrie; Johnson, Karen; 'karen.osborne@hsc.utah.edu'; 'ldw@iupui.edu'; 'mcollins@peds.uab.edu'; 'melissa.leps@utsouthwestern.edu'; 'monica.konstantino@yale.edu'; nancy newman; 'Nancy.Miller@UTSouthwestern.edu'; Newman, Jamie; rbara@med.wayne.edu; 'Michelle Tidwell'; 'Shirley Cosby'; 'Poundstone, Margaret '; 'Kimberley A Fisher'; 'Everett-Thomas, Ruth'; 'Rich, Wade'; 'npeters@wfubmc.edu'; 'Reubens, Linda'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: Support Trial Oximeter Returns

Dear all,

Now that the Support trial has completed enrollment and as your remaining infants complete the study per protocol; please return the study Masimo oximeters to their original institutions (Oximeter owner in the attached pdf file). Please also find attached an updated address list (Support Coordinator file attached) to include addresses for Miami, Wake Forest, Rochester and UCSD. Please clean all equipment and include sensors and probes prior to sending them home. For those oximeters currently being repaired at Masimo, please send the original institution an email listing the serial number being repaired and send that oximeter on once received back from Masimo.

Thank you all very much,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762

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kzaterka@rti.org
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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
Brown University	Angelita Hensman, R.N.C. Department of Pediatrics Women & Infant's Hospital 101 Dudley Street, Room 1136 Providence, RI 02905 ahensman@wihri.org (401) 274-1100 ext. 1730
Case Western Reserve University	Nancy Newman, R.N. University Hospitals Case Medical Center Rainbow Babies & Children's Hospital 11100 Euclid Ave., Room 3100 Cleveland, OH 44106-6010 nxs5@cwru.edu (216) 368-3084
Duke University	Kim Fisher, PhD, FNP, IBCLC Division of Neonatology Duke University Medical Center 204 Bell Building, Rm 141 Durham, NC 27710 foy00004@mc.duke.edu (919) 668-3360
Emory University	Ellen Hale, R.N.C., B.S. 3267 Sutcliffe Ridge Marietta, GA 30064 ellen_hale@oz.ped.emory.edu 678-232-7102.
Indiana University	Leslie Dawn Wilson, RN, BSN Research Manager Neonatal Network Coordinator Riley Hospital RR 208 699 West Dr Indianapolis, IN 46202 ldw@iupui.edu (317) 274-8255
Rochester University	Linda Reubens, R.N 601 Elmwood Ave., Box 651 Rochester, NY 14642 linda_reubens@urmc.rochester.edu (585) 275-0218

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
Stanford University	M. Bethany Ball Stanford University Division of Neonatology 750 Welch Road, Suite 315 Palo Alto, CA 94304 mbball@stanford.edu (650) 725-8342
Tufts University	Brenda MacKinnon, RNC, Floating Hospital for Children at Tufts Medical Center 800 Washington Street Newborn Medicine, Floating 2, Box 44 Boston, MA 02111 bmackinnon@tuftsmedicalcenter.org 617-636-1218; Beeper # (b)
University of Alabama	Monica Collins, RN, MaEd Division of Neonatology University of Alabama at Birmingham 525 New Hillman Building 619 South 19th St Birmingham, AL 35233 mcollins@peds.uab.edu (205) 934-5771
University of California, San Diego	Wade Rich University of California--San Diego 402 Dickerson St MPF 1-140 San Diego, CA 92103 wrich@ucsd.edu (619) 543-3759
University of Cincinnati	Cathy Grisby, R.N. Cincinnati Children's Hospital (S Building) 9th Floor/Room S9.303 240 Albert Sabin Way Cincinnati 45229-2842 grisbyca@email.uc.edu (513) 803-0950

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
University of Iowa	Karen J. Johnson, R.N. Department of Pediatrics University of Iowa 200 Hawkins Drive, 8900 JPP Iowa City, IA 52242 karen-johnson@uiowa.edu 319-356-2924
University of Miami	Ruth Everett-Thomas, PhD Central Building, Suite 740 Jackson Memorial Hospital 1611 NW 12 Avenue Miami, FL 33136 REverett@med.miami.edu (305) 585-6408
University of New Mexico	Conra Lacy, R.N. Department of Pediatrics 915 Camino de Salud NE Albuquerque NM 87131 cbackstrom@salud.unm.edu 505-272-0367
University of Texas – Dallas	Nancy Miller, R.N. and Melissa H. Leps, R.N. (Co-Coordinator) Department of Pediatrics University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., E3 404 Dallas, TX 75235-9063 Nancy.Miller@utsouthwestern.edu melissa.leps@utsouthwestern.edu (214) 648-3780
University of Texas – Houston	Georgia McDavid, R.N. Department of Pediatrics University of Texas-Houston 6431 Fannin, Suite 3.252, Medical Sciences Building Houston, TX 77030-1501 Georgia.E.McDavid@uth.tmc.edu (713) 500-5734

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
University of Utah	Karen Osborne, RN BSN Neonatal Research Network University of Utah The Williams Building Dept of Pediatrics, Division of Neonatology Salt Lake City, UT 84158 karen.osborne@hsc.utah.edu (801) 213-3298
Wayne State University	Becky Bara, RN, BSN or Division of Neonatal & Perinatal Medicine Children's Hospital of Michigan Dept. of Neonatology, #4C19 3901 Beaubien Blvd. Detroit, MI 48201 rbara@med.wayne.edu (313) 745-1436
Wake Forest University	Nancy Peters, R.N. Wake Forest University Health Sciences, Department of Pediatrics/Neonatology, Medical School Blvd. Winston-Salem, NC 27157 npeters@wfubmc.edu (336) 716-6911
Yale University	Monica Konstantino, R.N. Yale-New Haven Children's Hospital 20 York St. WP493 New Haven, CT 06504 monica.konstantino@yale.edu (203)688-7987

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Serial Numbers *Updated 1/31/08*	Color Codes	Oximeter Home (During study)	Oximeter Crystal (Right Ankle Sensor)
310716	BLUE	CENTER 3	CENTER 3
310725	ORANGE	CENTER 3	CENTER 3
310878	BLUE	CENTER 3	CENTER 3
310879	ORANGE	CENTER 3	CENTER 3
310881	BLUE	CENTER 3	CENTER 3
310884	BLUE	CENTER 3	CENTER 3
310886	ORANGE	CENTER 3	CENTER 3
310949	ORANGE	CENTER 3	CENTER 3
323319	BLUE	CENTER 3	CENTER 3
323320	ORANGE	CENTER 3	CENTER 3
323321	BLUE	CENTER 3	CENTER 3
323325	BLUE	CENTER 3	CENTER 3
323326	BLUE	CENTER 3	CENTER 3
323328	BLUE	CENTER 3	CENTER 3
310906	ORANGE	CENTER 4	CENTER 4
311179	BLUE	CENTER 4	CENTER 4
311194	ORANGE	CENTER 4	CENTER 4
311217	ORANGE	CENTER 4	CENTER 4
311320	ORANGE	CENTER 4	CENTER 4
311384	BLUE	CENTER 4	CENTER 4
311438	BLUE	CENTER 4	CENTER 4
311440	BLUE	CENTER 4	CENTER 4
313007	BLUE	CENTER 5	CENTER 5
313415	ORANGE	CENTER 5	CENTER 5
313468	ORANGE	CENTER 5	CENTER 5
313469	ORANGE	CENTER 5	CENTER 5
313470	BLUE	CENTER 5	CENTER 5
313471	BLUE	CENTER 5	CENTER 5
313542	ORANGE	CENTER 5	CENTER 5
313554	ORANGE	CENTER 5	CENTER 5
313560	ORANGE	CENTER 5	CENTER 5
313580	BLUE	CENTER 5	CENTER 5
313586	BLUE	CENTER 5	CENTER 5
313713	BLUE	CENTER 5	CENTER 5
313042	BLUE	CENTER 9	CENTER 9
313055	BLUE	CENTER 9	CENTER 9
313058	ORANGE	CENTER 9	CENTER 9
313072	BLUE	CENTER 9	CENTER 9
313082	BLUE	CENTER 9	CENTER 9
313085	ORANGE	CENTER 9	CENTER 9
313086	ORANGE	CENTER 9	CENTER 9
313089	ORANGE	CENTER 9	CENTER 9
313092	BLUE	CENTER 9	CENTER 9
313186	ORANGE	CENTER 9	CENTER 9
323078	ORANGE	CENTER 9	CENTER 9
323085	BLUE	CENTER 9	CENTER 9
323086	ORANGE	CENTER 9	CENTER 9
323087	BLUE	CENTER 9	CENTER 9
310719	ORANGE	CENTER 11	CENTER 11
310720	BLUE	CENTER 11	CENTER 11
310730	ORANGE	CENTER 11	CENTER 11
310744	BLUE	CENTER 11	CENTER 11
310749	BLUE	CENTER 11	CENTER 11
310751	BLUE	CENTER 11	CENTER 11
310762	ORANGE	CENTER 11	CENTER 11
310771	ORANGE	CENTER 11	CENTER 11
310778	BLUE	CENTER 11	CENTER 11
310805	BLUE	CENTER 11	CENTER 11
310882	ORANGE	CENTER 11	CENTER 11

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310885	BLUE	CENTER 11	[redacted]
310931	BLUE	CENTER 11	[redacted]
310947	ORANGE	CENTER 11	[redacted]
310948	ORANGE	CENTER 11	[redacted]
311019	ORANGE	CENTER 11	[redacted]
302324	BLUE	CENTER 12	[redacted]
311695	BLUE	CENTER 12	[redacted]
312058	BLUE	CENTER 12	[redacted]
312163	ORANGE	CENTER 12	[redacted]
312169	ORANGE	CENTER 12	[redacted]
312196	ORANGE	CENTER 12	[redacted]
312198	ORANGE	CENTER 12	[redacted]
312200	BLUE	CENTER 12	[redacted]
312203	BLUE	CENTER 12	[redacted]
312228	ORANGE	CENTER 12	[redacted]
312235	BLUE	CENTER 12	[redacted]
312250	ORANGE	CENTER 12	[redacted]
312251	ORANGE	CENTER 12	[redacted]
312333	BLUE	CENTER 12	[redacted]
312334	ORANGE	CENTER 12	[redacted]
312341	BLUE	CENTER 12	[redacted]
310828	ORANGE	CENTER 13	[redacted]
310896	BLUE	CENTER 13	[redacted]
310936	BLUE	CENTER 13	[redacted]
310969	ORANGE	CENTER 13	[redacted]
311002	ORANGE	CENTER 13	[redacted]
311128	ORANGE	CENTER 13	[redacted]
311203	ORANGE	CENTER 13	[redacted]
311319	BLUE	CENTER 13	[redacted]
311344	ORANGE	CENTER 13	[redacted]
311388	BLUE	CENTER 13	[redacted]
311411	BLUE	CENTER 13	[redacted]
311467	BLUE	CENTER 13	[redacted]
310241	BLUE	CENTER 14	[redacted]
310718	ORANGE	CENTER 14	[redacted]
310721	BLUE	CENTER 14	[redacted]
310726	BLUE	CENTER 14	[redacted]
310743	ORANGE	CENTER 14	[redacted]
310757	ORANGE	CENTER 14	[redacted]
310775	BLUE	CENTER 14	[redacted]
310916	ORANGE	CENTER 14	[redacted]
310930	ORANGE	CENTER 14	[redacted]
310932	BLUE	CENTER 14	[redacted]
310933	ORANGE	CENTER 14	[redacted]
310952	BLUE	CENTER 14	[redacted]
313019	BLUE	CENTER 14	[redacted]
313361	ORANGE	CENTER 14	[redacted]
313408	ORANGE	CENTER 14	[redacted]
313540	BLUE	CENTER 14	[redacted]
313558	BLUE	CENTER 14	[redacted]
313584	ORANGE	CENTER 14	[redacted]
338426	ORANGE	CENTER 14	[redacted]
338427	BLUE	CENTER 14	[redacted]
338428	ORANGE	CENTER 14	[redacted]
338429	BLUE	CENTER 14	[redacted]
311617	ORANGE	CENTER 15	[redacted]
311681	BLUE	CENTER 15	[redacted]
311777	BLUE	CENTER 15	[redacted]
311788	ORANGE	CENTER 15	[redacted]
312051	ORANGE	CENTER 15	[redacted]
312232	BLUE	CENTER 15	[redacted]

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312244	ORANGE	CENTER 15	
312247	BLUE	CENTER 15	
311530	BLUE	CENTER 16	
311557	ORANGE	CENTER 16	
311576	ORANGE	CENTER 16	
312095	BLUE	CENTER 16	
312116	ORANGE	CENTER 16	
312119	BLUE	CENTER 16	
312125	BLUE	CENTER 16	
312131	BLUE	CENTER 16	
312133	ORANGE	CENTER 16	
312172	ORANGE	CENTER 16	
312192	ORANGE	CENTER 16	
312214	ORANGE	CENTER 16	
312225	BLUE	CENTER 16	
312229	ORANGE	CENTER 16	
312233	BLUE	CENTER 16	
312242	ORANGE	CENTER 16	
312260	ORANGE	CENTER 16	
312268	BLUE	CENTER 16	
312272	BLUE	CENTER 16	
312283	BLUE	CENTER 16	
317219	BLUE	CENTER 16	
317227	ORANGE	CENTER 16	
317363	BLUE	CENTER 16	
317384	ORANGE	CENTER 16	
317420	BLUE	CENTER 16	
317431	BLUE	CENTER 16	
317438	ORANGE	CENTER 16	
317560	ORANGE	CENTER 16	
310562	BLUE	CENTER 18	
310727	ORANGE	CENTER 18	
310818	BLUE	CENTER 18	
310821	BLUE	CENTER 18	
310836	ORANGE	CENTER 18	
310839	ORANGE	CENTER 18	
310862	BLUE	CENTER 18	
310869	ORANGE	CENTER 18	
310873	ORANGE	CENTER 18	
310877	BLUE	CENTER 18	
310888	BLUE	CENTER 18	
310893	BLUE	CENTER 18	
310894	ORANGE	CENTER 18	
310951	BLUE	CENTER 18	
310985	ORANGE	CENTER 18	
311144	ORANGE	CENTER 18	
311158	ORANGE	CENTER 18	
311159	BLUE	CENTER 18	
310998	BLUE	CENTER 19	
311004	ORANGE	CENTER 19	
315452	BLUE	CENTER 19	
316381	BLUE	CENTER 19	
316382	ORANGE	CENTER 19	
316506	BLUE	CENTER 19	
316611	ORANGE	CENTER 19	
316774	BLUE	CENTER 19	
316779	BLUE	CENTER 19	
316783	ORANGE	CENTER 19	
316790	ORANGE	CENTER 19	
310937	BLUE	CENTER 22	
310989	BLUE	CENTER 22	

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310846	ORANGE	CENTER 22	[redacted]
310912	BLUE	CENTER 22	[redacted]
310914	BLUE	CENTER 22	[redacted]
310939	BLUE	CENTER 22	[redacted]
310944	BLUE	CENTER 22	[redacted]
310945	BLUE	CENTER 22	[redacted]
310958	ORANGE	CENTER 22	[redacted]
310962	BLUE	CENTER 22	[redacted]
318351	BLUE	CENTER 22	[redacted]
318859	BLUE	CENTER 22	[redacted]
323322	ORANGE	CENTER 22	[redacted]
323323	ORANGE	CENTER 22	[redacted]
323324	ORANGE	CENTER 22	[redacted]
323327	ORANGE	CENTER 22	[redacted]
310834	ORANGE	CENTER 23	[redacted]
310838	ORANGE	CENTER 23	[redacted]
310983	ORANGE	CENTER 23	[redacted]
311139	ORANGE	CENTER 23	[redacted]
317217	ORANGE	CENTER 23	[redacted]
317393	BLUE	CENTER 23	[redacted]
317398	ORANGE	CENTER 23	[redacted]
317399	ORANGE	CENTER 23	[redacted]
317408	BLUE	CENTER 23	[redacted]
310717	BLUE	CENTER 24	[redacted]
310723	ORANGE	CENTER 24	[redacted]
310724	ORANGE	CENTER 24	[redacted]
310729	ORANGE	CENTER 24	[redacted]
310734	BLUE	CENTER 24	[redacted]
310748	BLUE	CENTER 24	[redacted]
310874	ORANGE	CENTER 24	[redacted]
310913	BLUE	CENTER 24	[redacted]
317312	BLUE	CENTER 24	[redacted]
317427	ORANGE	CENTER 24	[redacted]
317443	BLUE	CENTER 24	[redacted]
320283	BLUE	CENTER 24	[redacted]
323024	ORANGE	CENTER 24	[redacted]
310820	ORANGE	CENTER 25	[redacted]
310826	ORANGE	CENTER 25	[redacted]
310850	ORANGE	CENTER 25	[redacted]
310875	BLUE	CENTER 25	[redacted]
310892	ORANGE	CENTER 25	[redacted]
310943	ORANGE	CENTER 25	[redacted]
310963	BLUE	CENTER 25	[redacted]
310974	ORANGE	CENTER 25	[redacted]
310994	BLUE	CENTER 25	[redacted]
310997	BLUE	CENTER 25	[redacted]
311138	ORANGE	CENTER 25	[redacted]
311145	BLUE	CENTER 25	[redacted]
311146	BLUE	CENTER 25	[redacted]
318358	ORANGE	CENTER 25	[redacted]
318364	ORANGE	CENTER 25	[redacted]
318389	BLUE	CENTER 25	[redacted]
318541	ORANGE	CENTER 25	[redacted]
318550	BLUE	CENTER 25	[redacted]
318844	ORANGE	CENTER 25	[redacted]
318848	BLUE	CENTER 25	[redacted]
318849	ORANGE	CENTER 25	[redacted]
320520	ORANGE	CENTER 25	[redacted]
320521	ORANGE	CENTER 25	[redacted]
320524	BLUE	CENTER 25	[redacted]
320525	BLUE	CENTER 25	[redacted]

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320526	ORANGE	CENTER 25	CENTER 22
320527	BLUE	CENTER 25	CENTER 22
320528	BLUE	CENTER 25	CENTER 22
320529	BLUE	CENTER 25	CENTER 22
320530	ORANGE	CENTER 25	CENTER 22
320531	ORANGE	CENTER 25	CENTER 22
328935	BLUE	CENTER 26	CENTER 16
328981	BLUE	CENTER 26	CENTER 16
329083	BLUE	CENTER 26	CENTER 16
329168	BLUE	CENTER 26	CENTER 16
329207	BLUE	CENTER 26	CENTER 16
329689	ORANGE	CENTER 26	CENTER 16
329703	ORANGE	CENTER 26	CENTER 16
329706	ORANGE	CENTER 26	CENTER 16
329709	ORANGE	CENTER 26	CENTER 16
329713	ORANGE	CENTER 26	CENTER 16
311157	ORANGE	MISSING	CENTER 22

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From: Gloria Siaw
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Ronald N Goldberg; Ricki F Goldstein; Kimberley.fisher@duke.edu; Melody B Lohmeyer; Gantz, Marie
Subject: Re: SUPPORT
Date: Tuesday, May 12, 2009 5:21:06 PM

Hi Rose,
We have resloved the outstanding missing data form SUPPORT. We have informed the mother of subject (b) (6) to see an ophthalmologist and awaiting to hear from subject's mother.

Thanks,

CENTER NETWORK ROP_message		
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Completed
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Completed
19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
CENTER NETWORK FU_message		
19	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. **Completed**

Gloria Siaw, BSN, CRA
Clinical Research Coordinator
Dept of Pediatrics/Neonatology
2424 Erwin Road - Suite 504
DUMC Box 2739
Durham, NC 27705
Phone: 919 - 681- 5859
Pager: 919-970(b) (6)
Fax: 919 - 681- 4868
Email: - gloria.siaw@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

05/08/2009 11:43 AM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, <gloria.siaw@duke.edu>, <Kimberley.fisher@duke.edu>, "Melody B Lohmeyer" <lohme001@mc.duke.edu>
cc "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,

We are missing some SUPPORT primary outcomes. **Recruitment is finished in the trial and we are trying to get all of the**

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needed information into the DMS in a timely manner.

Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
19	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
CENTER	NETWORK	FU_message
19	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Evans, Patricia W
Subject: RE: SUPPORT
Date: Monday, May 11, 2009 12:42:03 PM

Rose,

Patient (b) (6) is still pending. I am hoping to schedule her within the next month.

PS I am the follow-up coordinator if you'd like to add me to the list for this study. Thanks!

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713.500.6813 (office)
713.500.5794 (fax)
713.76(b) (6) (pager)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Evans, Patricia W
Sent: Monday, May 11, 2009 11:37 AM
To: Poundstone, Margaret
Subject: FW: SUPPORT
Importance: High

Just forwarding since you're not on the list.

Patricia W. Evans, MD
Assistant Professor of Pediatrics, Division of Neonatology
The University of Texas Medical School at Houston
713-500-5311 (office)
713-500-5794 (fax)
Patricia.W.Evans@uth.tmc.edu (e-mail)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 08, 2009 10:40 AM
To: Kennedy, Kathleen A; Tyson, Jon E; Evans, Patricia W; Mcdavid, Georgia E
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,

We are missing some SUPPORT primary outcomes. **Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner.** Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; bss5@cwru.edu; "nancy newman"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: RE: SUPPORT
Date: Monday, May 11, 2009 10:02:46 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 08, 2009 9:53 AM
To: mcw3@cwru.edu; bss5@cwru.edu; nancy newman
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing some SUPPORT primary outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

THIS IS AMAZING GIVEN YOUR FABULOUS RECRUITMENT!!!

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
3	[redacted]-done	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
3	[redacted] Came for appt., waited 2 hours, then left	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	[redacted] app[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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higginsr@mail.nih.gov

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From: Bridge, Renee
To: Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, May 08, 2009 4:21:03 PM

I have just entered the phy01 and finally the supp10 for (b) (6). I will transmitt the info now. Renee

From: Rich, Wade
Sent: Friday, May 08, 2009 9:01 AM
To: Bridge, Renee
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 08, 2009 8:43 AM
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing some SUPPORT primary outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose
CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

22

(b) (6)

PHY01 is expected based on NG07 but has not been entered.

Rosemary D. Higgins, MD

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Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B; Hamer, Faithe Angeline
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT
Date: Friday, May 08, 2009 3:01:29 PM

Hi. Please see below:

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b)(6)1 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 08, 2009 11:28 AM
To: Poindexter, Brenda B; Wilson, Leslie Dawn; Hamer, Faithe Angeline; Dusick, Anna M.
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT
Importance: High

Hi,
We are missing some SUPPORT primary outcomes. Recruitment is finished in the trial and we are trying to get all of the needed information into the DMS in a timely manner. Please let us know how you are doing.

Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported. Out pt information has been requested. Follow-up appt to be scheduled
12	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early. You will have this information in next transmission
CENTER	NETWORK	BPD_message
12	(b) (6)	Infant was eligible for challenge (per PHY01) but outcome was not entered on PHY02RA. You will have this information in next transmission.
12	(b) (6)1	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Infant is still in hospital.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Infant is still in hospital
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Infant is still in hospital
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Infant is still in hospital
CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. Scheduled home visit for next week
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. Scheduled home visit for next week

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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6100 Executive Blvd., Room 4B03
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higginsr@mail.nih.gov

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Thursday, May 07, 2009 3:05:32 PM
Attachments: Infants with missing outcomes 05-06-09.xls

Rose,

Attached is the list of infants who are missing SUPPORT primary outcomes this week.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

CENTER	NETWORK	ROP_message
3	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
12		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
14		The patient is within their Fol-up window and final ROP status has not been reported.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
23		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: FW: Support Trial Protocol
Date: Wednesday, May 06, 2009 8:01:28 PM
Attachments: RE Support Trial Protocol 1.htm
RE Support Trial Protocol 2 .htm

Hi Rose

I am forwarding this to you to think about with me. Jane was trying to be inclusive and asked Chuck Green for input as to order of tests, need for breaks, etc for the 6-7 year SUPPORT follow-up. This is what she got in return. I have not (and do not plan to) respond to this. Read especially email #1.

Other psychologists in the Network have been very helpful and supportive, and we have had a lot of input (including international) on this.

Let me know what you think. I told Jane not to worry about it for now - and not to rock the boat further. We may just choose to ignore the whole thing - that might be best.

Susan

Delivered-To: srhintz@stanford.edu
Subject: FW: Support Trial Protocol
Date: Mon, 4 May 2009 21:39:19 -0400
Thread-Topic: Support Trial Protocol
Thread-Index:
AcnKYzL7Dseiu3YZQRqGwkuz3lS0lwABchfwAAAl+EAACg+HIACjWeaw
From: "Hammond, Jane" <hammond@rti.org>
To: "Susan Hintz" <srhintz@stanford.edu>

Chuck has a slightly different way of approaching things. You will want to read through e-mail #1. I didn't respond to it and then I got e-mail #2. I didn't respond to that one either.

I don't want to alienate Jon Tyson, so just let me know how you would like to handle this. I've been out of the office so I do have an excuse for not responding to him earlier !

Jane

Jane A. Hammond, Ph.D.

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Transdisciplinary Behavioral Science Program

RTI International

6110 Executive Blvd, Suite 902

Rockville, Maryland 20852

301-770-8207 - phone

301-230-4646 - fax

Content-Type: text/html;
name="RE Support Trial Protocol 1.htm"
Content-Description: RE Support Trial Protocol 1.htm
Content-Disposition: attachment;
filename="RE Support Trial Protocol 1.htm"

Content-Type: text/html;
name="RE Support Trial Protocol 2 .htm"
Content-Description: RE Support Trial Protocol 2 .htm
Content-Disposition: attachment;
filename="RE Support Trial Protocol 2 .htm"

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From: Green, Charles [Charles.Green@uth.tmc.edu]
Sent: Friday, May 01, 2009 3:27 PM
To: Hammond, Jane
Cc: Tyson, Jon E
Subject: RE: Support Trial Protocol

No. Your e-mail was perfectly clear. The protocol is characterized as lengthy and intense in your original e-mail. I will not comment on either the appropriateness of the battery or its ordering unless I know the specific hypotheses for testing referral. I cannot provide input without that information. I either expect it to be furnished, or I expect not to be asked.

Dr. Green

From: Hammond, Jane [mailto:hammond@rti.org]
Sent: Friday, May 01, 2009 9:39 AM
To: Green, Charles
Subject: RE: Support Trial Protocol

Sorry – I guess my e-mail wasn't clear. Based on your experience in a clinic setting with kids, we are looking for your input on order of administration and breaks – things that would help the visit progress smoothly. Also, if you have suggestions on how to arrange the parent questionnaires, we would like to hear that too.

From: Green, Charles [mailto:Charles.Green@uth.tmc.edu]
Sent: Friday, May 01, 2009 10:29 AM
To: Hammond, Jane
Subject: RE: Support Trial Protocol

Jane,

The planned tests are really quite broad in scope. If possible could I have a set of the specific hypotheses for the study? In particular it would be helpful to have hypotheses related to both brain structure and function.

Thanks,

Chuck

From: Hammond, Jane [mailto:hammond@rti.org]
Sent: Friday, May 01, 2009 8:46 AM
To: Green, Charles
Subject: Support Trial Protocol

Hi Charles

As you know, the NRN SUPPORT Trial group is doing a follow-up study of kids in the 6-7 yr old range. Susan Hintz, the study PI, and I would appreciate it if you would review this grid *for the proposed order of the tests.* It is clear that we will need to have a substantial break for the children - like a lunch break - given the length and intensity of the testing, but we would like your input on order of admin, breaks, etc. based on your experience. The parent questionnaires can be administered simultaneously with the child testing. These questionnaires are not in any particular order right now, but perhaps you have suggestions on that.

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If you could let me know your thoughts in the next couple days, that would be great. I am compiling comments from the gold standard folks from the HIE study and will send everything on to Susan.

Thanks
Jane

Jane A. Hammond, Ph.D.
Transdisciplinary Behavioral Science Program
RTI International
6110 Executive Blvd, Suite 902
Rockville, Maryland 20852
301-770-8207 - phone
301-230-4646 - fax

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From: Green, Charles [Charles.Green@uth.tmc.edu]
Sent: Friday, May 01, 2009 4:11 PM
To: Hammond, Jane
Cc: Tyson, Jon E
Subject: RE: Support Trial Protocol

On reflection I think my e-mail was a bit abrupt. I still require the information to provide my input, but I want you to understand why. Cognitive assessments are done to obtain a sample of behavior from a child in order to infer to the "population" of that child's behavior. This is very similar to the type of reasoning applied in inferential statistics. In so far as the sample of the child's behavior is representative of the population, accurate inferences are possible. Anything that degrades the sample of child behavior by definition degrades the inferences. These things include fatigue, external noise and distractions, in short anything that interferes with the cognitive processing under investigation. It is important to organize testing in two ways: 1) to systematically vector in on the cognitive function in question, ruling out other process that may be confounding inference, and 2) to prioritize testing such that the most highly valued data is gathered prior to inevitable degradation of performance due to fatigue. Further, depending on the hypotheses other cognitive processing, effects should be considered that might bias interpretation of norms. It might be that all batteries follow the same ordering....it might be that there are scenarios where counterbalancing order across participants is of interest. Finally, depending on what cognitive functions are of interest there may be a pre-defined order of administration that is required.

Chuck

From: Hammond, Jane [mailto:hammond@rti.org]
Sent: Friday, May 01, 2009 9:39 AM
To: Green, Charles
Subject: RE: Support Trial Protocol

Sorry – I guess my e-mail wasn't clear. Based on your experience in a clinic setting with kids, we are looking for your input on order of administration and breaks – things that would help the visit progress smoothly. Also, if you have suggestions on how to arrange the parent questionnaires, we would like to hear that too.

From: Green, Charles [mailto:Charles.Green@uth.tmc.edu]
Sent: Friday, May 01, 2009 10:29 AM
To: Hammond, Jane
Subject: RE: Support Trial Protocol

Jane,

The planned tests are really quite broad in scope. If possible could I have a set of the specific hypotheses for the study? In particular it would be helpful to have hypotheses related to both brain structure and function.

Thanks,

Chuck

From: Hammond, Jane [mailto:hammond@rti.org]
Sent: Friday, May 01, 2009 8:46 AM
To: Green, Charles
Subject: Support Trial Protocol

Hi Charles

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As you know, the NRN SUPPORT Trial group is doing a follow-up study of kids in the 6-7 yr old range. Susan Hintz, the study PI, and I would appreciate it if you would review this grid *for the proposed order of the tests.* It is clear that we will need to have a substantial break for the children - like a lunch break - given the length and intensity of the testing, but we would like your input on order of admin, breaks, etc. based on your experience. The parent questionnaires can be administered simultaneously with the child testing. These questionnaires are not in any particular order right now, but perhaps you have suggestions on that.

If you could let me know your thoughts in the next couple days, that would be great. I am compiling comments from the gold standard folks from the HIE study and will send everything on to Susan.

Thanks
Jane

Jane A. Hammond, Ph.D.
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301-230-4646 - fax

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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter; Pablo Sanchez
Subject: Re: SUPPORT death
Date: Monday, May 04, 2009 4:22:41 PM

A SUPPORT baby (NRN #(b) (6)) died (b) (6). The death was not due to the study. This infant was over 9 months old and was a DNR due to multiple medical problems.(b) (6) (b) (6). The MedWatch is pending.
Please contact me if you have any questions.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

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From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Friday, May 01, 2009 10:20:54 AM

The completed NG03 and NG07 forms aren't technically expected until the patient reaches status (120 days, death or discharge), but the PHY01 form is expected on the 36 week date of the patient. For Support patients, this form is still required, so she should be getting this information regarding BPD at the 36 week date and thus could complete it out in the NG03 and NG07 data.

Let me know if this prompts any further questions.
Jenny

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 01, 2009 10:13 AM
To: Gantz, Marie; Auman, Jeanette O.
Subject: Fw: SUPPORT

Does BPD get put in at 36 weeks from children who remain in the hospital??
Rosemary D. Higgins, MD
Program Scientist
NICHD

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Gantz, Marie ; Hamer, Faithe Angeline
Sent: Fri May 01 10:09:32 2009
Subject: RE: SUPPORT

Hi. I am a bit confused as to why the network is expecting data (NG03 and NG07) on infants because they have reached 36 weeks. Both of these forms are unable to be completed until the pt is discharged or has reached 120 days. Am I not understanding what you are expecting?

(b) (6) -Pt has been "no show" for ROP visits. They are still working on getting them in. We are awaiting one ROP visit outcome which should be arriving soon from 2008, but we do not think it will be the final one.
(b) (6) -BPD challenge being entered and have chart has been ordered for ROP status
(b) (6) -Infant is still in the hospital
(b) (6) -Infant is still in the hospital
(b) (6) -Data has been entered
(b) (6) -Infant is still in the hospital
(b) (6) -Data has been entered

Thank you-

Leslie Dawn Wilson, BSN, CCRC
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.[redacted] (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:59 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
12	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
CENTER	NETWORK	BPD_message
12	(b) (6)	Infant was eligible for challenge (per PHY01) but outcome was not entered on PHY02RA.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
12	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
12	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 has not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Mcdavid, Georgia E
To: Higgins, Rosemary (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; Archer, Stephanie (NIH/NICHD) [E]; "Cunningham, Meg"
Cc: Kennedy, Kathleen A
Subject: Support death
Date: Thursday, April 30, 2009 5:40:21 PM

Patient (b) (6) expired (b) (6) DOB was (b) (6) and the infant was randomized in to the SUPPORT study. The infant received SOC. The infant was removed from the ventilator (b) (6) after receiving lengthy courses of (b) (6) with no improvement. Medwatch to follow.

Georgia McDavid, R.N.
Senior Research Nurse-pediatrics/neonatology
Nurse Coordinator - NICHD Neonatal Network
MSB 3.252
office: 713-500-5734
office fax: 713-500-5794

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From: Gantz, Marie
To: Johnson, Karen; Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Thursday, April 30, 2009 12:48:03 PM

Karen,

We do have the PHY02BASE and PHY02REDU forms for infant (b) (6), but we don't have the PHY02RA which includes the variable that says whether or not the challenge was passed. The missing PHY02RA is noted in the last round of batch edits you received on the website.

Let me know if you have any questions.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
(b) (6)

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Thursday, April 30, 2009 11:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT

Rose and Marie,
(b) (6) – PHY02 was entered on (b) (6). I'm not sure why it shows as missing?
(b) (6) and 65682 have repeatedly not shown for appointments! ☹ I have entered as not obtained at follow-up. Their window has now closed.
(b) (6) data will be in next transmission.
Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (319) 354(b) (6) ask for page(b) (6)

"Far and away the best prize that life offers is the chance to work hard at work worth doing." Theodore Roosevelt

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:24 PM
To: Bell, Edward; Johnson, Karen
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
24	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
24	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
CENTER	NETWORK	BPD_message
24	(b) (6)	Infant was eligible for challenge (per PHY01) but outcome was not entered on PHY02RA.
24	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20892
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; mgantz@rti.org
Cc: Pickett, James; Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Tuesday, April 28, 2009 6:39:35 PM

James is currently working with the Center to try to figure out why their transmission has failed.

Thanks,
Jenny

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 28, 2009 6:38 PM
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin; Gantz, Marie
Subject: Fw: SUPPORT

Can you look into the transmission issue?
Rosemary D. Higgins, MD
Program Scientist
NICHD

----- Original Message -----
From: Bridge, Renee <rbridge@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Tue Apr 28 17:50:58 2009
Subject: RE: SUPPORT

I have entered all the current info that I have. There seems to be an issue with our tranmission of data that we are working on. So, in a nutshell. Patient(b) (6) was lost to follow-up, therefore N was entered on the Supp 10 form. Same for patient(b) (6). I corrected patient(b) (6) to reflect that the infant was on RA, no cannula or cpap at 36 weeks, but went on to be discharged on oxygen. The NGO7 will show this info. I am still trying one more thing for Patient(b) (6) for ROP status. So, as soon as we are able to trasmit, the info will be there. Sorry for the delays. Renee

---

From: Rich, Wade
Sent: Monday, April 27, 2009 12:43 PM
To: Bridge, Renee
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 1:11 PM
To: Finer, Neil; Rich, Wade
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to

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be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

Thanks for all your hard work.

Rose
CENTER

NETWORK

ROP_message

22

(b) (6)

The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

22

(b) (6)

No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

CENTER

NETWORK

BPD_message

22

(b) (6)

NG07 36 week snapshot is entered but highest FiO2 status at 36 weeks is missing

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From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, April 28, 2009 6:34:26 AM

Rose,
This baby is still in house. Do you want it in as of now or can it wait until discharge which should be this week?
Thanks,
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper #(b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 4:22 PM
To: Frantz, Ivan; Mackinnon, Brenda
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

Thanks for all your hard work.

Rose

CENTER	NETWORK	BPD_message
23	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

Rosemary D. Higgins, MD
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From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, April 27, 2009 2:36:36 PM

Rose,

Patient (b) (6) has not been seen yet. Mom has had some personal medical issues, which have delayed the visit. I hope to schedule her within the next month.

Thanks!

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713.500.6813 (office)
713.500.5794 (fax)
713.760(b) (6) (pager)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Evans, Patricia W
Sent: Friday, April 24, 2009 10:32 PM
To: Poundstone, Margaret
Subject: FW: SUPPORT

Checking on the status of the SUPPORT kid. You can e-mail Rose directly or e-mail me and I'll reply. Thanks so much,

Patricia

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:07 PM
To: Kennedy, Kathleen A; Tyson, Jon E; Evans, Patricia W; Mcdavid, Georgia E
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
18	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

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From: Hale, Ellen
To: Higgins, Rosemary (NIH/NICHD) [E]; Ellen Hale; Barbara Stoll; Ira Adams-Chapman
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Monday, April 27, 2009 3:21:39 PM

Rose,
Has been a fairly constructive day and I'm making progress. See my comments below. Will let you know as I progress.
Thanks for all your help,
Ellen

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:55 PM
To: Hale, Ellen; Ellen Hale; Barbara Stoll; Ira Adams-Chapman
Cc: Gantz, Marie
Subject: SUPPORT

Hi,

We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.

I was aware of a transmission problem from your site – let me know if this is still a problem.

Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status. You have sent email to Dale.
9	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders. Has been entered. Lost to F/U--somewhere in Mexico.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Trying to locate child. Has never been seen in DPC since discharge.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Private opth office has been called. Waiting for fax.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Final visit entered -- mature.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Still looking.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Still looking.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Moved to Lousiana and currently cannot locate. Still looking.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Final visit entered -- mature.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Why did this mom only bring one twin for eye appointment? Have left message for mom to make appointment for this child.

CENTER	NETWORK	BPD_message
9	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. Child was on a vent at 36 weeks. Remains in hosp and not yet 120 days.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed. Has missed 3 appointments. Should be seen May 8?!?
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. Seen 4/14 -- awaiting all forms.

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9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. All forms entered.
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. Awaiting forms.
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. Seen 4/16 -- awaiting forms.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, April 27, 2009 11:03:20 AM

Yes, he turned up 3 days later.
A neighbor told her to scatter kitty litter from the litter box in the yard so he could recognize the scent and find the house.
He showed up about 6 hours later!

Thanks for asking!
Bonnie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 27, 2009 10:41 AM
To: Bonnie Siner
Cc: mcw3@case.edu; nancy newman
Subject: RE: SUPPORT

Bonnie
Thanks (Did your (b) (6)

Also, if (b) (6) was entered prior to last Tuesday (April21) – it is NOT in the DMS system, if later, it should show up in this week's run

Thanks
Rose

From: Bonnie Siner [mailto:bss5@case.edu]
Sent: Monday, April 27, 2009 10:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@case.edu; 'nancy newman'
Subject: RE: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:50 PM
To: Michelle Walsh; Bonnie Siner; nancy newman
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.
This is outstanding given your incredible recruitment!!!!!
Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders. DONE, NEEDS TO BE ENTERED.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. FOLLOW-UP APPT.SCHEDULED FOR 4/30/09.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. FOLLOW-UP APPT.SCHEDULED FOR 5/28/09.

CENTER	NETWORK	BPD_message
3	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. WORKING ON IT TODAY.
3	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. ALREADY ENTERED.

Rosemary D. Higgins, MD
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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@case.edu; "nancy newman"
Subject: RE: SUPPORT
Date: Monday, April 27, 2009 10:24:51 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 24, 2009 3:50 PM
To: Michelle Walsh; Bonnie Siner; nancy newman
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing the following SUPPORT primary outcomes and would like to be able to perform that analysis shortly after the final patients reach status. Please promptly attend to these missing data elements.
This is outstanding given your incredible recruitment!!!!!
Thanks for all your hard work.

Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders. DONE, NEEDS TO BE ENTERED.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. FOLLOW-UP APPT.SCHEDULED FOR 4/30/09.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. FOLLOW-UP APPT.SCHEDULED FOR 5/28/09.

CENTER	NETWORK	BPD_message
3	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. WORKING ON IT TODAY.
3	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered. ALREADY ENTERED.

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Friday, April 24, 2009 10:21:44 AM
Attachments: Infants with missing outcomes 04-23-09.xls

Rose,

Here is the list of infants with missing SUPPORT outcomes this week.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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CENTER	NETWORK	ROP_message
3	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The patient is within their Fol-up window and final ROP status has not been reported.
12		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
16		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
16		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
18		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10. Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
19		The patient is within their Fol-up window and final ROP status has not been reported.
22		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.

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From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; nfiner@ucsd.edu; Abhik Das (adas@rti.org)
Cc: Navarrete, Cristina; "Marie Gantz"
Subject: 4 22 SUPPORT Growth Sec Possible Tables_Figures_Analysis
Date: Thursday, April 23, 2009 1:17:42 PM
Attachments: 4 22 SUPPORT Growth Sec Possible Tables_Figures_Analysis.docx

Hi all,

Good to be on the call yesterday. As promised, here is an outline of the analytical plan, with questions at appropriate points. Please let the sub-committee see the suggested analysis plan and let us have your feedback. As mentioned yesterday, your expected timeline for analysis to begin is towards the end of summer.

Thanks
Shahnaz

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SUPPORT: GROWTH SECONDARY STUDY

Oxygen Saturation Arm (randomized from birth, stratified into 24-25 and 26-27w):

- LOW Saturation = 85-89%
- HIGH Saturation= 91-95%

Hypotheses
PRIMARY Low O_2saturation infants better short AND long term growth
PRIMARY Low O_2saturation infants better in-hospital growth trajectory
SECONDARY Independent of saturation group, infants >50% time daily median sats within 85-95% better growth (while on supplemental O2) [redacted]
SECONDARY Independent of saturation group, infants with BPD poorer short and long term growth
SECONDARY Independent of saturation group, positive correlation between better long term growth and better ND outcome

Specific Aims	Data
1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age	Weight, HC, Length at: Birth day 7 day 14 day 21 day 28 32wk PMA 36wk PMA OR discharge 18-22month follow-up
2. To determine nutritional intake (parenteral and enteral) during hospital stay	24h intake (enteral/parenteral): volume and composition (kcal/kg/d) day 7 day 14 day 21 day 28 32wk PMA 36wk PMA OR discharge
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first	<10th%ile at PMA 36 OR discharge

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	(proposed reference growth curve: NICHD 1999 Ehrenkranz postnatal growth curves)
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age	<10th%ile at 18-22month follow-up (proposed reference growth curve: NCHS/CDC)
5. To determine in-hospital growth velocity/trajectory in low and high saturation arms	Antropometrics from birth to PMA 36 OR discharge (6 time points)OR between EACH measurement period WT: gain of grams/day HC: gain of cm/week Length: gain of cm/week *need time interval from birth to PMA 36w or discharge *time interval from 28d and 32wk WILL BE DIFFERENT ACCORDING TO GA AT BIRTH
6. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms	Antropometrics at discharge and 18-22m FU (2 time points) *need time interval from discharge to 18-22m FU WILL BE DIFFERENT FOR EACH
7. To determine growth in relation to the proportion of time spent with oxygen saturation a. <85% and >95% (out of range) b. 85-95% (within range)	Subanalysis of the two groups: Combine exposure groups and then split each according to 1. >50% of time within range 2. <50% of time within range
8. To determine growth in relation to the proportion of infants with a. Median SpO2>95% b. Median SpO2 between 85-95% c. Median SpO2 <85%	Subanalysis of the two groups: Combine exposure groups and then split to overall saturation median value a. Higher than upper limit

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	b. Within range c. Lower than lower limit
9. To relate incidence of BPD in low and high saturation arms to growth	Subanalysis of the two groups: a. BPD b. No BPD
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms	Change in anthropometrics and Neurodevelopmental measures (Bayley III: cognitive, language, motor)

POPULATION:

SUPPORT Cohort minus ~300 (enrolled prior to initiation of secondary),

?+/- deaths prior to 36wk/ discharge (short term analysis)

?minus lost to follow-up (long term analysis) +/- deaths

TABLE: POPULATION CHARACTERISTICS (GDB data)

Population Characteristics:	LOW Saturation	HIGH Saturation	Statistic Comparison
N			
Birth weight			t test
Gestational Age			t test
%SGA			Chi-square
Head Circumference at birth <10%			Chi-square
Length at birth <10%			Chi-square
Race (black, not black)			Chi-square
Multiple birth (yes, no)			Chi-square
Antenatal steroids (yes, no)			Chi-square
Method of delivery (SVD, not SVD)			Chi-square
Mother education: HS grad (yes, no)			Chi-square

TABLE: CLINICAL CHARACTERISTICS (GDB and SUPPORT data)

Clinical Characteristics:	LOW Saturation	HIGH Saturation	Statistic Comparison
N			
RDS (yes, no)			Chi-square
BPD (yes, no)			Chi-square
PDA (yes, no)			Chi-square
IVH/PVL (yes, no)			Chi-square

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Postnatal Steroids for BPD (yes, no)			Chi-square
Sepsis (yes, no)			Chi-square
NEC (yes, no)			Chi-square
Duration of Mech Vent (d)			t-test
Duration of suppl O2 (d)			t-test
% Mortality at 36wk PMA			Chi-square

TABLE: NUTRITIONAL INTAKE (GRO and GDB data)

Energy Intake (kcal/kg/d)	LOW Saturation	HIGH Saturation	Statistic Comparison
Day 7 total			Repeated measures ANOVA?
Day 14 total			
Day 21 total			
Day 28 total			
32 wk PMA			
36wk PMA			
Age at first enteral feed			t-test
Age at full enteral feed			t-test
Duration of PN≥75%			t-test

PRIMARY OUTCOMES:

TABLE AND/OR FIGURE: GROWTH OUTCOMES

a. absolute numbers for W/L/HC for each time point

b. z-scores for W/L/HC for each time point (reference growth curve: Ehrenkranz 1999 NICHD longitudinal postnatal growth chart) to demonstrate how far they deviate from the mean OR <10th%ile to demonstate proportion of growth failure at each time point

Absolute numbers vs. z-score vs. <10th%ile (W/L/HC)	LOW Saturation	HIGH Saturation	
Birth			
Day 7			
Day 14			
Day 21			
Day 28			
32wk PMA			
36wk PMA			
18-22m FU			

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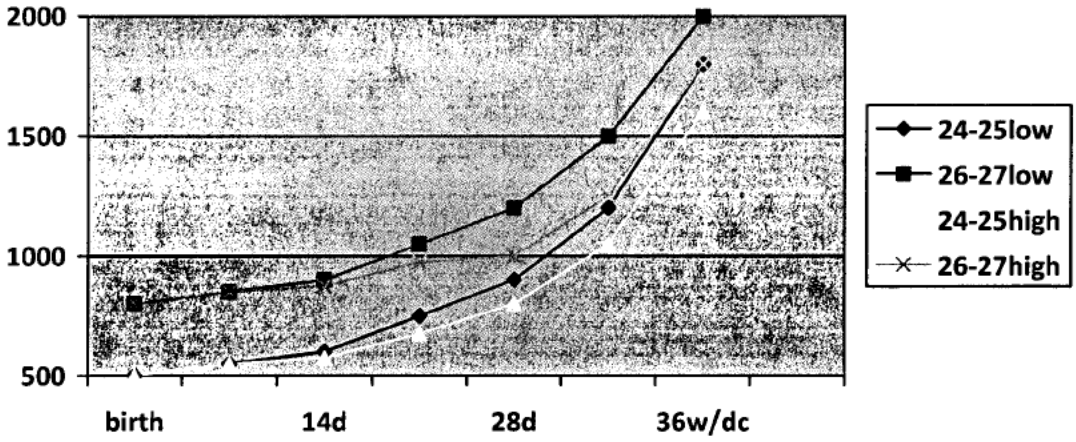
GROWTH OUTCOMES at 36wk PMA and at 18-22m ASSESSED BY Odds Ratios for INFANTS in LOW vs HIGH SATS by Logistic Regression (adjusting for confounders in population characteristics/clinical characteristics/nutritional intake univariate analyses + plus study center+death)

	LOW Saturation	HIGH Saturation	OR (95% CI)
36wk PMA			
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			
18-22m F/U			
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			

LONGITUDINAL GROWTH ANALYSIS BY HIERARCHICAL MODELING (Multilevel-regression analysis) similar to NICHD Ehrenkranz 1999 where growth is first analyzed over time and then by exposure.

??? Stratify analysis according to 24-25 and 26-27wks???

(FIGURE with plots of change in wt/time for each period)



Growth Velocity table OR graph: wt gain/d or L and HC gain/wk;

SECONDARY HYPOTHESES:

FIGURE: Description of duration of time of median sats within or outside target range.....

GROWTH OUTCOMES at 36wk PMA and at 18-22m ASSESSED BY Odds Ratio for INFANTS >50% within target saturation range vs. <50% within target saturation range (while on supplemental O2) (adjusting

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for confounders in population characteristics/clinical characteristics/nutritional intake univariate analyses+ plus study center+death)

	>50% Median Sats within range (85-95%)	<50% Median Sats within range	OR (95% CI)
36wk PMA			
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			
18-22m F/U			
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			

LONGITUDINAL GROWTH ANALYSIS BY HIERARCHICAL MODELING (Multilevel-regression analysis) for INFANTS >50% within target saturation range vs. <50% within target saturation range

GROWTH OUTCOMES at 36wk PMA and at 18-22m ASSESSED BY Odds Ratio for INFANTS according to median saturation values (while on supplemental O2) (adjusting for confounders in population characteristics/clinical characteristics/nutritional intake univariate analyses+ plus study center+death)

	Median Sats >95%	Median Sats 85-95%	Median Sats <85%	OR (95% CI)
36wk PMA				
Wt <10th%ile				
L< 10th%ile				
HC <10th%ile				
18-22m F/U				
Wt <10th%ile				
L< 10th%ile				
HC <10th%ile				

LONGITUDINAL GROWTH ANALYSIS BY HIERARCHICAL MODELING (Multilevel-regression analysis) for INFANTS according to median saturation values (while on supplemental O2)

GROWTH OUTCOMES at 36wk PMA and at 18-22m ASSESSED BY Odds Ratio for INFANTS with BPD vs. INFANTS without BPD (adjusting for confounders in population characteristics/clinical characteristics/nutritional intake univariate analyses+death)

	BPD	No BPD	OR (95% CI)
36wk PMA			
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			
18-22m F/U			
Wt <10th%ile			

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L< 10th%ile			
HC <10th%ile			

LONGITUDINAL GROWTH ANALYSIS BY HIERARCHICAL MODELING (Multilevel-regression analysis) for INFANTS with BPD vs. INFANTS without BPD

GROWTH OUTCOMES and NEURO-DEVELOPMENTAL OUTCOME at 18-22m BY Odds Ratio (adjusting for confounders in population characteristics/clinical characteristics/nutritional intake univariate analyses+death)

	Cognitive <70	Language Comp <70	Motor Comp <70
Wt <10th%ile			
L< 10th%ile			
HC <10th%ile			

GROWTH:

- Short Term = in hospital (*need time interval from birth to PMA 36w or discharge)
- Long Term = 18-22m follow-up (*need time interval from discharge to 18-22m F/U)

DEFINITION OF GROWTH:

Most commonly used measure for growth failure is <10th %ile at each time point; therefore, growth may be defined as any parameter ≥10th %ile

BOOST uses <10th%ile for wt and L and <3rd%ile for HC (in comparison to NCHS growth curves)

Glutamine Growth 2005 <10th and 5th%ile

Velocity= difference of parameter between two (adjacent) time points and divided by the number of days between the measurements. What is the definition of good growth velocity? Standard definitions of accepted wt gain 15/kg/day or L and HC gain 0.9cm/wk

STOP-ROP uses change in growth parameter between two time points (absolute value)

NICHD (Ehrenkranz 1999) provides growth velocity by BW intervals

Standard Deviation Score for each time point

PN malnutrition (Embleton 2001) uses change in z-score (in relation to birth z score)

NICHD (Ehrenkranz 1999) also provides average body weight vs. PMA in weeks

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WHICH REFERENCE GROWTH CHART TO USE?

In-hospital:

Ehrenkranz 1999 NICHD longitudinal postnatal growth chart: 1994-1995 501-1500g up to 120d (n=1660)

Fenton 2003 (fetal-infant chart: meta-analysis or combination of published fetal reference charts and smoothed onto the CDC term infant chart)

(Glutamine Growth 2006: used Alexander as growth reference)

Long-term 18-22m F/U:

NCHS (National Center for Health Statistics) aka.CDC

(NICHD Glutamine Growth 2006: used NCHS as growth reference)

(NICHD Infection and Growth/ND 2004: used NCHS as growth reference)

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From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]; Navarrete, Cristina
Cc: "mcunningham@rti.org"
Subject: Re: SUPPORT Call
Date: Wednesday, April 22, 2009 9:48:40 AM

That sounds good. Tina and I have thought about the analysis plan and will have suggestions for the call. We had a brief call with RTI/Marie Gantz last week to discuss approach.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Navarrete, Cristina; Duara, Shahnaz
Cc: Cunningham, Meg
Sent: Wed Apr 22 09:44:23 2009
Subject: FW: SUPPORT Call

If you have specific agenda items, please send them. Otherwise we can review enrollment in the main trial, enrollment in the secondary study and potential areas for data checks (i.e. missing data elements that will affect the analysis). We can also discuss analysis plans

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Wednesday, April 22, 2009 9:39 AM
To: Webb, Robin E.; sduara@miami.edu; CNavarrete@med.miami.edu; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Call

Reminder for today's call.

From: Webb, Robin E.
Sent: Tuesday, March 17, 2009 10:35 AM
To: Webb, Robin E.; 'sduara@miami.edu'; 'CNavarrete@med.miami.edu'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'
Cc: '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin
Subject: SUPPORT Call

The call to discuss the growth secondary study has been scheduled for:

Wednesday, 4/22

11:00am ET

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Dial:

Within the USA

866-675(b) (6)

or

Outside the USA

1-203-310(b) (6)

Then, enter Participant Passcode:

(b) (6)

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From: Cunningham, Meg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SC Agenda
Date: Tuesday, April 21, 2009 12:51:37 PM
Attachments: SC_Meeting_JUNE2009_Agenda.doc

Here it is so far. We are full.

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org

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NICHD Neonatal Research Network Steering Committee June 25, 2009 Bolger Center, Potomac, MD	
8:00-9:00am(1hr)➔ Rm	**Early BP Subcommittee**
9:00-9:45am (45min)➔ Rm	**Concept:** Use of Ethyl Nitrite(ENO) to Prevent BPD – Dr. Auten – via phone
9:45-10:30am(45min)➔ Rm	**Concept:** A randomized trial of recombinant granulocyte-colony stimulating factor and intravenous immunoglobulin for infants with gram negative or serious bloodstream infection – Dr. Schelonka
10:30-11:15am(45min)➔ Rm	**Concept:** Does delivery of inhaled nitric oxide via Jet Ventilation offer an advantage to the term/late-preterm infant with respiratory failure – Dr. Sokol
11:15-12:15pm (1hr)➔ Rm	**Inositol** (Phelps, Ehrenkranz, Goldberg, Poindexter, Laptook, Goldberg, Watterberg, Frantz, Ward, Higgins, Das, Baxter, Ball, Backstrom-Lacy)
12:15-1:00pm ➔	**Lunch**
1:00-3:00pm(2 hrs)➔ Rm	**NEST Training**
3:00-3:45pm(45 min)➔ Rm	**Concept:** aEEG – Dr. Van Meurs
3:45-4:30pm(45min)➔ Rm	**PROTOCOL:** tin mesoporphyrin – Dr. Tyson
4:30-5:15pm (45min) ➔ Rm	**Concept:** aEEG – Dr. Van Meurs
5:15-6:15pm(1hr)➔ Rm	**Concept:** potential NIRS study – Dr. Chock

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NICHD Neonatal Research Network Steering Committee
June 26, 2009 Bolger Center, Potomac, MD

Room

8:00 AM	Welcome	Dr. Caplan
8:05 AM	Inositol	Dr. Phelps
8:20 AM	Candida	Dr. Benjamin
8:35 AM	Cytokines	Dr. Carlo
8:50 AM	Protocol Review	Dr. Ehrenkranz
9:00 AM	Genomics	Dr. Goldberg (Murray via phone)
9:15 AM	Preemie aEEG	Dr. Davis
9:30 AM	Hypotension	Dr. Fernandez
9:45 AM	Preemie iNO	Dr. Van Meurs
9:50 AM	Coordinators	
9:55 AM	6-24 Hour Hypothermia	Dr. Laptook
10:10 AM	NEC – lap vs. drain	Dr. Blakely
10:25 AM	SUPPORT	Dr. Finer (via phone)
11:40 AM	Phototherapy	Dr. Morris/Tyson
11:10 AM	Publications	Dr. Carlo
11:20 AM	EOS Surveillance	Dr. Stoll
11:30 PM	GDB	Dr. Stoll
11:40 AM	PCV-7	Dr. D'Angio
12:10 PM	Lunch	
1:00 PM	Probiotics	Dr. Oh
1:15 PM	Hypothermia FU/aEEG	Dr. Shankaran
1:30 PM	Follow-up Study	Dr. Vohr
1:35 PM	6-7 SUPPORT	Dr. Hintz
1:50 PM	Early BP	Dr. Batton
2:05 PM	**Concept**: Comprehensive Care	Dr. Evans
2:50 PM	New Business	

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From: Laptook, Abbot
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT two-site ancillary
Date: Monday, April 20, 2009 4:21:03 PM

I am a yes after reading Michele's explanation. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 13, 2009 3:29 PM
To: nfiner@ucsd.edu; mcw3@cwru.edu; Wally Carlo, M.D.; kurt.schibler@cchmc.org; Laptook, Abbot; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; mcunningham@rti.org
Subject: SUPPORT two-site ancillary

Hi,
Attached is a **confidential** proposal from Drs. Martin and DiFiore to look at desaturations and ROP from the SUPPORT trial oximeters at UCSD and Rainbow Babies. Michele had mentioned this study on our last conference call.
There are currently SUPPORT trial oxygen saturation data in 95 infants from the Cleveland site and 14 potential infants from the San Diego site with 2 second resolution. As described in the grant proposal entitled *INTERMITTENT HYPOXIA AND RETINOPATHY OF PREMATURITY*, the investigators are requesting access to the randomization assignment for these infants. In addition, they are requesting the software code (from RTI or Masimo) to correct the modified/blinded SaO2 data back to the true values. If this software is not available, they will need access to the documentation containing the details of how the points were modified. This information will be needed to write the software code at our site.

PLEASE SEND ME A YES/NO VOTE by April 20 to allow submission of the proposal with the caveat that the primary paper(s) be accepted for publication prior to any release of information.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
Cc: Pablo Sanchez
Subject: Re: SUPPORT death
Date: Friday, April 17, 2009 11:44:27 AM

SUPPORT baby NN#(b) (6), with (b) (6), was taken off the vent. yesterday at the parent's request. The Medwatch is pending. The death was not due to the SUPPORT Study.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

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From: Julie Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: rxm6@case.edu
Subject: RE: Desaturation vs ROP grant
Date: Tuesday, April 14, 2009 9:36:07 AM

Thank you for the information. I will discuss this with Richard and Chris to see if this is something that we can pursue.

Regards,

Julie

At 09:26 AM 4/14/2009, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> I sent the request to the SUPPORT Subcommittee yesterday and will be in touch with you regarding their interest shortly.
>
> Also, as I mentioned on the phone, NICHD has approved the following concept (see http://www.nichd.nih.gov/funding/strategies_concepts/2009/concepts_january.cfm)
>
> **Safe and Effective Instruments and Devices for use in the Neonatal ICU**
>
> **January 2009**
>
> A Request for Applications proposed entitled, "**Safe and Effective Instruments and Devices for use in the Neonatal ICU**" using the Small Business Technology Transfer Research (STTR) and the Small Business Innovative Research (SBIR) mechanisms.
>
> **Purpose**
> Although neonatal intensive care is heavily dependent on modern technology, there is paucity of efforts in research and development (R&D) directed at improving existing technologies, or in developing innovative devices and instruments for use in the neonatal ICU. The purpose of the proposed RFA is thus to foster collaborative research between bioengineering and biomedical scientific communities that can lead to improvements in existing technologies, as well as introduction of innovative instruments and devices that are safe and effective.
>
> **Scope**
> The scope of the RFA will be to solicit applications that address developing devices for use in the neonatal period. Projects should be related, but not limited, to the following general topics. Devices and instruments for: 1) assessing cardiopulmonary functions (blood pressure, cardiac output, and pulmonary functions); 2) cerebral oxygenation and optical imaging of the brain; 3) continuous monitoring of glucose and other blood chemistry parameters; 4) rapid diagnosis of sepsis; and 5) catheters and tubes that reduce or prevent the incidence of thrombus formation, and reduce healthcare-associated infections by reducing bacterial and fungal colonization.
>
> **Objectives**
> Devices and instruments developed for use in the sick newborn infants should be based on sound bioengineering principles and tested appropriately in clinical settings for their safety profiles and accuracy of functioning. The objective is to foster continued collaboration between biomedical and bioengineering communities in the field of pediatric device development, leading to a set of safe and effective instruments and devices that can be used while caring for sick newborn infants.
>
> **Program Contact**
> Tonse N. K. Raju, MD
> Medical Officer
> Pregnancy and Perinatology Branch
> CDBPM
> Regards
> Rose

From: Julie Di Fiore [mailto:jmd3@case.edu]

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Sent: Monday, April 13, 2009 9:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: rxm6@case.edu
Subject: Desaturation vs ROP grant

Dear Dr. Higgins,

We currently have SUPPORT trial oxygen saturation data in 95 infants from the Cleveland site and 14 potential infants from the San Diego site with 2 second resolution. As described in our grant proposal entitled *INTERMITTENT HYPOXIA AND RETINOPATHY OF PREMATURITY*, we are requesting access to the randomization assignment for these infants. In addition, we are requesting the software code (from RTI or Masimo) to correct the modified/blinded SaO2 data back to the true values. If this software is not available, we will need access to the documentation containing the details of how the points were modified. This information will be needed to write the software code at our site.

Best Regards,

Julie

Juliann Di Fiore
Research Engineer
Division of Neonatology
Rainbow Babies & Children's Hospital
11100 Euclid Ave.
Cleveland, OH 44106
(216) 844-1478
Fax: (216) 844-3380

Juliann Di Fiore
Research Engineer
Division of Neonatology
Rainbow Babies & Children's Hospital
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Cleveland, OH 44106
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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT two-site ancillary
Date: Tuesday, April 14, 2009 8:22:07 AM

Hi Rose,
I vote Yes. Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
USA
TEL: 513-862-3007
PAGER: 513-736-[redacted]
E-mail: kurt.schibler@cchmc.org

On 4/13/09 3:28 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
> Attached is a **confidential** proposal from Drs. Martin and DiFiore to look at desaturations and ROP from the SUPPORT trial oximeters at UCSD and Rainbow Babies. Michele had mentioned this study on our last conference call.
> There are currently SUPPORT trial oxygen saturation data in 95 infants from the Cleveland site and 14 potential infants from the San Diego site with 2 second resolution. As described in the grant proposal entitled *INTERMITTENT HYPOXIA AND RETINOPATHY OF PREMATURITY*, the investigators are requesting access to the randomization assignment for these infants. In addition, they are requesting the software code (from RTI or Masimo) to correct the modified/blinded SaO2 data back to the true values. If this software is not available, they will need access to the documentation containing the details of how the points were modified. This information will be needed to write the software code at our site.
>
> **PLEASE SEND ME A YES/NO VOTE by April 20** to allow submission of the proposal with the caveat that the primary paper(s) be accepted for publication prior to any release of information.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
> National Institutesof Health
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> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT two-site ancillary
Date: Monday, April 13, 2009 6:13:11 PM

I vote yes!

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 13, 2009 6:01 PM
To: Walsh, Michele
Subject: Re: SUPPORT two-site ancillary

Michele
I have 3 yeses so far, 0 no
Rosemary D. Higgins, MD
Program Scientist
NICHD

From: Walsh, Michele
To: Wally Carlo, M.D. ; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu ; mcw3@cwru.edu ; kurt.schibler@cchmc.org ; Laptook, Abbot ; Bradley Yoder ; Roger.Faix@hsc.utah.edu ; Das, Abhik ; nancy newman ; Rich, Wade ; Gantz, Marie ; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin ; mcunningham@rti.org
Sent: Mon Apr 13 17:39:25 2009
Subject: RE: SUPPORT two-site ancillary
Just to be clear: we are asking for a letter of support from the NRN steering committee
That states if an R21 submission to develop methodologies is funded, there would be access to this data set.
The goal is to develop better methods for analyzing
the complex data contained in the saturation files:
Should one time average, is it better to look at the lowest sat, highest sat,
Are swings in saturation more meaningful, etc.
No specific hypotheses would be tested in this methodologic work-
Rather it is just to advance the field's methods for analyzing this complex data.
WE have 82 patients that were not in SUPPORT. WE would utilize the SUPPORT data
Set for testing after we develop methods in the non-SUPPORT cohort.
Thanks!

Michele Walsh
beeper (b) (6)
Ph 216 844 3759

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, April 13, 2009 3:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mcw3@cwru.edu; kurt.schibler@cchmc.org; Laptook, Abbot; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; mcunningham@rti.org
Subject: RE: SUPPORT two-site ancillary

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I vote YES.

I am concerned about bias but I think they should be encouraged to study this. There should be a much more specific hypothesis as well as many very well pre-specified hypotheses as they want rather than exploratory analyses.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 13, 2009 2:29 PM
To: nfiner@ucsd.edu; mcw3@cwru.edu; Wally Carlo, M.D.; kurt.schibler@cchmc.org; Laptook, Abbot; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; mcunningham@rti.org
Subject: SUPPORT two-site ancillary

Hi,
Attached is a **confidential** proposal from Drs. Martin and DiFiore to look at desaturations and ROP from the SUPPORT trial oximeters at UCSD and Rainbow Babies. Michele had mentioned this study on our last conference call.
There are currently SUPPORT trial oxygen saturation data in 95 infants from the Cleveland site and 14 potential infants from the San Diego site with 2 second resolution. As described in the grant proposal entitled *INTERMITTENT HYPOXIA AND RETINOPATHY OF PREMATURITY*, the investigators are requesting access to the randomization assignment for these infants. In addition, they are requesting the software code (from RTI or Masimo) to correct the modified/blinded SaO2 data back to the true values. If this software is not available, they will need access to the documentation containing the details of how the points were modified. This information will be needed to write the software code at our site.

PLEASE SEND ME A YES/NO VOTE by April 20 to allow submission of the proposal with the caveat that the primary paper(s) be accepted for publication prior to any release of information.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch

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Blansfield, Earl (NIH/NICHD) [E]

From: Hale, Ellen <ehale@emory.edu>
Sent: Friday, April 10, 2009 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose,
We are having transmission issues and James and I have been trying to correct things.
Some things already taken care of and working on the rest. Thanks for all the reminders.
Have a Happy Easter,
Ellen

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, April 10, 2009 12:06 PM
To: Hale, Ellen; Barbara Stoll; Ira Adams-Chapman; Ellen Hale; Susie Buchter
Cc: mgfuller@ucsd.edu
Subject: SUPPORT

Hi,

We are missing SUPPORT outcomes on the following infants. Let us know how you are doing. Thanks for all the effort!

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not o
done		
9	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not o
done		
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit

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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die
	done	
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
	done	
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit
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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for eit

CENTER	NETWORK	BPD_message
9	(b) (6)	PHY01 is expected based on NG07 but has not been entered.
	done	
9	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
	done	

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9	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
	still in hospital.	

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
	Has 3rd appt. scheduled.	
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
	done	
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.
	exams done &waiting for forms	

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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National Institutesof Health

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From: Adams-Chapman, Ira
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, April 10, 2009 12:24:49 PM

Hi Rose,
Will check with Ellen and Michelle on Monday- I think that everyone is off today for Good Friday. These eye exams are a challenge but will follow-up and verify status.
Thanks,
Ira

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, April 10, 2009 12:06 PM
To: Adams-Chapman, Ira; Barbara Stoll; Ira Adams-Chapman; Ellen Hale; Susie Buchter
Cc: mgfuller@ucsd.edu
Subject: SUPPORT

Hi,

We are missing SUPPORT outcomes on the following infants. Let us know how you are doing. Thanks for all the effort!

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	BPD_message
9	(b) (6)	PHY01 is expected based on NG07 but has not been entered.
9	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.
9	(b) (6)	Date of 36 weeks PMA has been reached but NG03 and NG07 have not been entered.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

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9 (b)(6) FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Thursday, April 09, 2009 12:06:29 PM
Attachments: Infants with missing outcomes 04-08-09.xls

Rose,

Attached are the reminders for SUPPORT infants who are missing outcomes this week. I have added the reminders for infants who have reached 36 weeks PMA but who do not have the NG03 or NG07 entered. I have also added some reminders for infants whose FU windows have closed but who do not have final ROP outcome reported.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP message
3	(b) (6)	The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
12		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
14		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
16		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
16		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 (lowest zone of any vessles is II at last exam). Also, SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age; please change answer to missing.
19		The patient is within their Fol-up window and final ROP status has not been reported.
22		The pt's FU window has closed and final ROP status has not been reported. If final ROP status was not obtained at FU, answer SUPP10 Q:'Final ROP status determined at 18M FU'=N to avoid further reminders.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT preemie central MRI reading
Date: Tuesday, April 07, 2009 11:33:39 PM

Wow -(b) (6) ! (b) (6) ! Congrats!

Susan

On Apr 7, 2009, at 6:12 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov > wrote:

> Susan
> The week of May 18 looks good. For Memorial Day weekend, my (b) (6)
> May 29- June 2 - i am attending a meeting in new mexico
> June 15-(b) (6)
>
> Let me know what the best options are for Pat
>
> Thanks
> Rose
> Rosemary D. Higgins, MD
> Program Scientist
> NICHD
>
> ----- Original Message -----
> From: Susan Hintz <srhintz@stanford.edu>
> To: M Bethany Ball <mbball@stanford.edu>
> Cc: Kris Zaterka <zkaterka@rti.org>; adas@rti.org <adas@rti.org>;
> Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Tue Apr 07 15:48:56 2009
> Subject: Fwd: Re: SUPPORT preemie central MRI reading
>
> FYI - Sounds like Dr. Barnes is on board, but needs to check
> schedule. He says he prefers WEEKday - and then he could request
> academic time and could be relieved of clinical duties for that
> period of time.
>
> Susan
>
>> Delivered-To: srhintz@stanford.edu
>> Date: Tue, 7 Apr 2009 12:33:02 -0700 (PDT)
>> From: "Patrick David Barnes M.D." <pbarnes@stanford.edu>
>> To: Susan Hintz <srhintz@stanford.edu>
>> Subject: Re: SUPPORT preemie central MRI reading
>> X-Originating-IP: [10.252.10.32]
>>
>> Very good. will get back. I actually prefer during the week and
>> requesting specific academic time for this.
>> Pat B
>>
>> ----- Original Message -----
>> From: "Susan Hintz" <srhintz@stanford.edu>

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>> To: pbarnes@stanford.edu
>> Cc: "M Bethany Ball" <mbball@stanford.edu>, "Kris Zaterka"
>> <zkaterka@rti.org>, higginsr@mail.nih.gov, adas@rti.org,
>> vanmeurs@stanford.edu
>> Sent: Tuesday, April 7, 2009 11:26:00 AM GMT -08:00 US/Canada Pacific
>> Subject: SUPPORT preemie central MRI reading
>>
>>
>> Hi Pat,
>>
>>
>> Our wonderful data center for the Neonatal Research Network (RTI) is
>> busily in the process of making 500+ new and improved central reader
>> forms and packaging all the MRI disks for the SUPPORT study for your
>> enjoyment. They have also very graciously arranged for one of their
>> lead programmer/analysts (and maybe others from RTI to make things
>> even smoother) to be able to come out to Stanford for a few days to
>> at least get the process started, sit with you and take dictation
>> as you power through MRI readings. This will streamline the process
>> and also have someone there for both of us in case questions come up
>> about how data would be entered. Dr. Higgins, Program Scientist for
>> the Neonatal Research Network, may even be able to come for a day -
>>
>>
>> I am thinking that end of a week or a weekend might be a good time.
>> I know, not optimal for our lives, but things could get done more
>> quickly and without interruptions - this is how we are doing the
>> central cranial US reading. Given the time crunch and looming
>> deadlines, it would be great to get this going in May. We will all
>> be at the Pediatric Academic Societies meeting in Baltimore, then
>> the cranial US central reading in the beginning of May.
>>
>>
>> So I would suggest we look at our schedules for May 15-31, focusing
>> on the following weekend-spanning dates -
>>
>>
>> May 15-18
>> May 22-25 (yes, this is Memorial Day weekend)
>> May 29-31
>>
>>
>> I will be on service in NICU the next week and weekend (June 1-8),
>> but if that weekend (5-8) works for others, you could do it but I
>> won't be around much at all -
>>
>>
>> I will be out of town June 9 for 10 days.
>>
>>
>> Let me know your schedules in the next week - the team from RTI will
>> need to start making arrangements.
>>
>>
>> Susan
>>
>> --

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>> Susan R. Hintz, M.D., M.S. Epi
>> Associate Professor of Pediatrics
>> Division of Neonatal and Developmental Medicine
>> Stanford University School of Medicine
>> 750 Welch Road, Suite 315
>> Palo Alto, CA 94304
>> ph: 650-723-5711
>> fax: 650-725-8351
>
>

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: wrich@ucsd.edu
Subject: RE: SUPPORT infants with missing BPD or ROP
Date: Tuesday, April 07, 2009 9:11:52 AM

I will do that.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 06, 2009 9:11 PM
To: Gantz, Marie; nfiner@ucsd.edu
Cc: wrich@ucsd.edu
Subject: Re: SUPPORT infants with missing BPD or ROP

Add them to my list for the every 2 week reminders
Rosemary D. Higgins, MD
Program Scientist
NICHD

From: Gantz, Marie
To: Finer, Neil ; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Sent: Mon Apr 06 15:29:35 2009
Subject: RE: SUPPORT infants with missing BPD or ROP
Neil,

It could be that some of the 21 infants without NG03s still have not reached status. However, I can add reminders for the centers to enter the NG03s and NG07s to the list Rose sends out every 2 weeks, especially if birth occurred over 120 days ago.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, April 03, 2009 8:22 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT infants with missing BPD or ROP

Hi Marie

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It looks like # 3 in your attachment accounts for the majority of concerns – ie the 21 infants with no NGO3. We need clarity on these infants.

Any Baby with a Diagnosis of BPD does not require further so I would not add the infants in your #2 to the missing BPD outcomes list.

Thanks Marie

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 02, 2009 2:19 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT infants with missing BPD or ROP

Neil and Rose,

Attached is a document with details on infants missing BPD and ROP outcomes, including reasons the outcome is missing, current PMA and, for ROP, status and PMA at last exam.

There are a couple of things to note regarding missing BPD:

1) Currently there are 21 infants who have survived to 12 hours but who do not have a form NG03 entered. For the missing outcomes lists I have been sending to Rose, I have been keying off of the NG03; thus, these infants have not received missing BPD reminders. However, I can add them to the list if you wish.
2) There are some infants who should have a PHY01 based on their NG07 36 week snapshot data but who have a default BPD determination based on the NG07 (for example, if they were on vent or CPAP at 36 weeks then BPD=Y). These infants have not been receiving missing BPD reminders, and they do not appear on the attached list, because they have a BPD status based on the NG07. They have, however, been receiving missing forms reports from Jenny every two weeks to remind them that the PHY01 is expected. If you would like me to add these reminders to the missing BPD reminders that Rose sends out, I can do that.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Finer, Neil
To: "Gantz, Marie"
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT infants with missing BPD or ROP
Date: Monday, April 06, 2009 4:19:57 PM

Hi Marie
You're correct.
I think that those reminders would help clarify the status of these infants
Thanks
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, April 06, 2009 12:30 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT infants with missing BPD or ROP

Neil,

It could be that some of the 21 infants without NG03s still have not reached status. However, I can add reminders for the centers to enter the NG03s and NG07s to the list Rose sends out every 2 weeks, especially if birth occurred over 120 days ago.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, April 03, 2009 8:22 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT infants with missing BPD or ROP

Hi Marie

It looks like # 3 in your attachment accounts for the majority of concerns – ie the 21 infants with no NGO3. We need clarity on these infants.
Any Baby with a Diagnosis of BPD does not require further so I would not add the infants in your #2 to the missing BPD outcomes list.

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Thanks Marie
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 02, 2009 2:19 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT infants with missing BPD or ROP

Neil and Rose,

Attached is a document with details on infants missing BPD and ROP outcomes, including reasons the outcome is missing, current PMA and, for ROP, status and PMA at last exam.

There are a couple of things to note regarding missing BPD:

1) Currently there are 21 infants who have survived to 12 hours but who do not have a form NG03 entered. For the missing outcomes lists I have been sending to Rose, I have been keying off of the NG03; thus, these infants have not received missing BPD reminders. However, I can add them to the list if you wish.
2) There are some infants who should have a PHY01 based on their NG07 36 week snapshot data but who have a default BPD determination based on the NG07 (for example, if they were on vent or CPAP at 36 weeks then BPD=Y). These infants have not been receiving missing BPD reminders, and they do not appear on the attached list, because they have a BPD status based on the NG07. They have, however, been receiving missing forms reports from Jenny every two weeks to remind them that the PHY01 is expected. If you would like me to add these reminders to the missing BPD reminders that Rose sends out, I can do that.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Evans, Patricia W
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tyson, Jon E; Kennedy, Kathleen A
Subject: FW: SUPPORT
Date: Monday, April 06, 2009 12:53:05 PM

FYI.

Patricia W. Evans, MD
Assistant Professor of Pediatrics, Division of Neonatology
The University of Texas Medical School at Houston
713-500-5311 (office)
713-500-5794 (fax)
Patricia.W.Evans@uth.tmc.edu (e-mail)

Stop Raping our Greatest Resource: Power to Women in the DRC
To learn more about the plight of the women in the Congo and the doctor who is saving them, visit www.vday.org, listen to http://www.npr.org/templates/story/story.php?storyId=99838343, or watch http://newsite.vday.org/spotlight-video

---

From: Poundstone, Margaret
Sent: Monday, April 06, 2009 9:50 AM
To: Evans, Patricia W
Subject: RE: SUPPORT

(b) (6) will be seen this week (b) (6) has not been scheduled yet.

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713.500.6813 (office)
713.500.5794 (fax)
713.760(b) (pager)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Evans, Patricia W
Sent: Tuesday, March 31, 2009 12:58 AM
To: Poundstone, Margaret
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 3:38 PM
To: Kennedy, Kathleen A; Mcdavid, Georgia E; Tyson, Jon E; Evans, Patricia W
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Thanks
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
18	(b) (6)	The patient is within their FoI-up window and final ROP status has not been reported.
18	(b) (6)	The patient is within their FoI-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Bridge, Renee
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, April 03, 2009 1:26:58 PM

Dear Dr. Higgins, I apologize for not catching this problem many months, maybe years ago. I have printed the info from the follow up protocol (NF) forms on the patients that were entered there incorrectly. I will enter them in the SUPPORT protocol (SF) forms. I tried to delete the patients from Follow-up, but I do not think I can to this. Again, I am sorry for my ignorance. I think I finally got it....Renee The patient numbers are
(b) (6) [redacted]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 3/31/2009 1:41 PM
To: Bridge, Renee; Gantz, Marie
Cc: Rich, Wade
Subject: RE: SUPPORT

Marie-
Do we have the data on the missing forms listed below??
Thanks
Rose

-----Original Message-----
From: Bridge, Renee [mailto:rbridge@ucsd.edu]
Sent: Tuesday, March 31, 2009 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT

Dear Dr. Higgins, I am working on (b) (6) [redacted], but I checked the data entry for (b) (6) [redacted] and the missing forms are complete. Please let me know if you have other information. I am starting to go through each file to assess for missing info. Thank you. Renee Bridge, RN UCSD Neonatology

---

From: Rich, Wade
Sent: Monday, March 30, 2009 2:02 PM
To: Bridge, Renee
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

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Sent: Monday, March 30, 2009 1:44 PM
To: Finer, Neil; Rich, Wade; Vaucher, Yvonne; Fuller, Martha
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Thanks
Rose
CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

22

(b) (6)

No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

CENTER

NETWORK

FU_message

22

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

22

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03

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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Hamer, Faithe Angeline
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Herron, Dianne E; Wilson, Leslie Dawn; Poindexter, Brenda B
Subject: RE: SUPPORT
Date: Friday, April 03, 2009 11:29:00 AM

Rose -
Here are the following updates for the SUPPORT inquiries. We will continue to monitor the top three. Thanks!

(b) (6) - thank you for the heads up – we are aware and it is being followed.
- form is currently being worked on – will enter as soon as it is complete.
–awaiting clinic info; will update next week
- already entered and updated.

Faithe Hamer, BS
Riley Hospital for Children
NICHD Follow Up Coordinator
fahamer@iupui.edu (email)
278-7364 (phone)
278-7856 (fax)
312(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 4:35 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn; Dusick, Anna M.; Hamer, Faithe Angeline
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Thanks
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
12	(b) (6)	No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
12	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
CENTER	NETWORK	FU_message
12	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 has not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Susan Hintz
To: petrie@rti.org
Cc: kzaterka@rti.org; mcunningham@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: RE: CUS Central Reading
Date: Thursday, April 02, 2009 7:23:54 PM

From Tom Slovis - sounds like he is OK with the envelope packaging plan

Susan

Hi, sounds ok and don't remember! Tom

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thursday, April 02, 2009 3:16 PM
To: Cunningham, Meg
Cc: petrie@rti.org; kzaterka@rti.org; dbulas@cnmc.org; Slovis, Thomas; higginsr@mail.nih.gov
Subject: Re: CUS Central Reading

Hi all,

I am forwarding this to Drs. Bulas and Slovis - the email below pertains to how Dr. Barnes like the MRI's "packaged", so perhaps the central readers would like to weigh in on how they would like things set up.

Dorothy and Tom - for the MRI's, we have been individually "packaging" the disks of the imaging - along with a central reader form pre-populated with some of the data at the header - in a 9x12 envelope with the description of what the imaging is (in that case SUPPORT MRI, but in your case it would be SUPPORT CUS), NRN center #, patient #, and date imaging done. Then, Dr. Barnes has been "signing off" the front of the envelope when done.

If this sounds good to you as a way to pre-package the studies, we should alter it in the following way:

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1) Prepopulate TWO central reader forms and put them in the envelope along with the disk of the CUS

2) The envelope would be labeled "SUPPORT CUS", not SUPPORT MRI

3) When you read, the RTI assistant would take the form and disk out of the envelope, making sure not to show you the other form (i.e., if it's filled out by the other reader already). When you have completed reading, the RTI assistant or you could initial the front of the envelope - by the end, we would have 2 sign-offs on each envelope.

At least it would all be neatly packaged - but weigh in if you would like it some other way.

**The other question that has come up is in the header of the CUS central reader form (ATTACHED), question 3 - the question is "Reading" (not Reader, which is a different question). This same thing was on the PiNO CUS central reader form, and for the life of me I can't remember what it was for - was this for the initials of the RTI assistant that marked the form while the central reader read?? Dorothy, Tom or Carolyn - do you remember?

Thanks,

Susan

Susan R. Hintz, M.D., M.S. Epi

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Division of Neonatal and Developmental Medicine

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Hi Dr. Hintz,

I am working on getting all the materials for CUS central reading setup. Kris forwarded me the message below, is this how you would like the materials setup for the central reading? If you have any other requests, please let me know.

I am also going to attach forms to each CUS and pre-populate the following information:

Center

Network #

Reader

Date Read

Date of Sonogram

However, question 3 under section A is **Reading**. What information are we collecting in this field? Is this something that can be pre-populated on the form? Attached is the form for your reference.

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Thanks!

Meg

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, February 25, 2009 2:02 AM
To: Zaterka-Baxter, Kristin
Subject: Re: Support MRI secondary images for central reading

Yes, they should be sent asap. HOWEVER, before you start sending, I would love it if you could "package" them there the way Dr. Barnes likes it before you send them to me. Up to now, I have done it, but I simply don't have the time or support to do it now. This "packaging" is something he and I developed to make sure everything stays in the right place, and to make it as easy as possible for him to read efficiently. The process involves putting each individual CD along with a MRI scoring form *already marked with the patient number, site and date of exam on BOTH pages of the scoring form* in a 8x11 or 9x12 manila or white envelope Then, I label the front of the envelope with the title "SUPPORT MRI study", the patient study ID, the site #, the date of the MRI. So - I could take a picture of the front of the envelope and send it to you.

Also - do you have the newest version of the SUPPORT MRI scoring forms and key?

Thanks - let me know

Susan

Hi Susan,

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Now that Dr. Barnes has completed the Hypothermia MRI central readings do have a timeline for when you and Dr. Barnes would like to start receiving the Support MRIs?

Thanks,

Kris

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

P.O. Box 12194

RTP, NC 27709-2194 USA

(tel) 919-485-7750

(fax) 919.485.7762

kzaterka@rti.org

www.rti.org

Federal Express/UPS/DHL Shipping Address:

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

RTP, NC 27709 USA

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Content-Type: application/msword;
name="Central ReaderCranial US[MRI04]6-7-05.doc"
Content-Description: Central ReaderCranial US[MRI04]6-7-05.doc
Content-Disposition: attachment;
filename="Central ReaderCranial US[MRI04]6-7-05.doc"

Attachment converted: Macintosh HD:Central
ReaderCrania#20E22E.doc (WDBN/«IC») (0020E22E)

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From: Gantz, Marie
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT infants with missing BPD or ROP
Date: Thursday, April 02, 2009 5:19:04 PM
Attachments: SUPPORT infants with missing BPD or ROP 04-02-09.rtf

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Neil and Rose,

Attached is a document with details on infants missing BPD and ROP outcomes, including reasons the outcome is missing, current PMA and, for ROP, status and PMA at last exam.

There are a couple of things to note regarding missing BPD:

1) Currently there are 21 infants who have survived to 12 hours but who do not have a form NG03 entered. For the missing outcomes lists I have been sending to Rose, I have been keying off of the NG03; thus, these infants have not received missing BPD reminders. However, I can add them to the list if you wish.
2) There are some infants who should have a PHY01 based on their NG07 36 week snapshot data but who have a default BPD determination based on the NG07 (for example, if they were on vent or CPAP at 36 weeks then BPD=Y). These infants have not been receiving missing BPD reminders, and they do not appear on the attached list, because they have a BPD status based on the NG07. They have, however, been receiving missing forms reports from Jenny every two weeks to remind them that the PHY01 is expected. If you would like me to add these reminders to the missing BPD reminders that Rose sends out, I can do that.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Reasons BPD is missing

The FREQ Procedure

Reason no BPD classification				
nobpdreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0=NG02 not entered	8	11.43	8	11.43
1=Infant < 37 weeks PMA	37	52.86	45	64.29
2=survival to 12 hours temporarily missing on NG02	1	1.43	46	65.71
3=Infant alive at 12 hours but NG03 and NG07 not entered	21	30.00	67	95.71
4=Infant in hospital at 36 weeks but NG07 not entered	1	1.43	68	97.14
5=NG07 36 week snapshot missing data on FiO2 and RA by NC/CPAP/vent	1	1.43	69	98.57
6=Eligible for challenge per PHY01 but no PHY02RA result	1	1.43	70	100.00

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The FREQ Procedure

Reason no BPD classification=0=NG02 not entered

	Current estimated PMA			
Group	Frequency	Percent	Cumulative Frequency	Cumulative Percent
	8	100.00	8	100.00

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The FREQ Procedure

Reason no BPD classification=1=Infant <=37 weeks PMA

	Current estimated PMA			
estage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
29	1	2.70	1	2.70
30	2	5.41	3	8.11
31	5	13.51	8	21.62
32	4	10.81	12	32.43
33	1	2.70	13	35.14
34	10	27.03	23	62.16
35	10	27.03	33	89.19
36	2	5.41	35	94.59
37	2	5.41	37	100.00

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The FREQ Procedure

Reason no BPD classification=2=Survival to 12 hours temporarily missing on NG02

Current estimated PMA				
Level	Frequency	Percent	Cumulative Frequency	Cumulative Percent
24	1	100.00	1	100.00

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The FREQ Procedure

Reason no BPD classification=3=Infant alive at 12 hours but NG03 and NG07 not entered

	Current estimated PMA			
CStage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
38	3	14.29	3	14.29
39	4	19.05	7	33.33
40	3	14.29	10	47.62
41	2	9.52	12	57.14
42	2	9.52	14	66.67
43	2	9.52	16	76.19
45	2	9.52	18	85.71
46	1	4.76	19	90.48
48	1	4.76	20	95.24
63	1	4.76	21	100.00

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The FREQ Procedure

Reason no BPD classification=4=Infant in hospital at 36 weeks but NG07 not entered

Current estimated PMA				
cestage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
46	1	100.00	1	100.00

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The FREQ Procedure

Reason no BPD classification=5=NG07 36 week snapshot missing data on FiO2 and RA by NC/CPAP/vent

Current estimated PMA				
Catage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
58	1	100.00	1	100.00

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The FREQ Procedure

Reason no BPD classification=6=Eligible for challenge per PHY01 but no PHY02RA result

Current estimated PMA				
Change	Frequency	Percent	Cumulative Frequency	Cumulative Percent
42	1	100.00	1	100.00

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Reasons ROP is missing

The FREQ Procedure

Reason for no ROP classification: noropreason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
-7=Infant withdrawn	4	1.90	4	1.90
0=No NG02 data (Estimated PMA unknown)	7	3.32	11	5.21
1=Estimated PMA <55 weeks	82	38.86	93	44.08
2=Lowest zone of any vessels is I at last exam	2	0.95	95	45.02
3=Lowest zone of any vessels is II at last exam	57	27.01	152	72.04
4=Lowest zone of any vessels is III for one exam	55	26.07	207	98.10
5=PMA>=55 weeks but no ROP exams entered	4	1.90	211	100.00

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=2=Lowest zone of any vessels is I at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
1	33	3	P	1	P	174	Y		3=Closed
2	47	1	2	1	2	220	Y	N	3=Closed

Reason for no ROP classification=3=Lowest zone of any vessels is II at last exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at FU	FU window
3	37	2	2	2	2	55			1=Not open yet
4	38	2	2	2	2	55			1=Not open yet
5	34	2	2	2	2	57			1=Not open yet
6	37	2	2	3	2	57			1=Not open yet
7	33	2	2	2	2	58			1=Not open yet
8	32	2	.	2	.	58			1=Not open yet
9	36	2	2	2	2	59			1=Not open yet
10	35	2	2	2	2	60			1=Not open yet
11	39	2	2	2	2	60	Y	N	1=Not open yet
12	37	2	2	2	2	64			1=Not open yet
13	34	2	2	2	2	68			1=Not open yet
14	37	2	2	2	2	68		N	1=Not open yet
15	35	2	2	2	2	69			1=Not open yet
16	38	2	2	2	2	69			1=Not open yet
17	38	2	2	2	2	72			1=Not open yet
18	36	2	2	2	2	76			1=Not open yet
19	39	2	2	2	2	78			1=Not open yet
20	38	2	1	2	1	81	Y		1=Not open yet
21	49	2	3	2	3	86	Y		1=Not open yet
22	43	2	2	2	2	88			1=Not open yet
23	50	2	2	2	2	88	Y		1=Not open yet
24	44	2	2	2	2	88	Y		1=Not open yet
25	42	2	2	2	2	88		N	1=Not open yet
26	33	2	2	2	2	90	Y		1=Not open yet
27	38	2	2	2	2	91	Y		1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels previous exam	Current estimated PMA	Acute ROP status OS at FU at 55 weeks PMA	Final ROP status obtained at	Final window
28	36	2	2	2	2	92			1=Not open yet
29	41	2	2	2	2	96	Y		1=Not open yet
30	38	2	2	2	2	98			1=Not open yet
31	36	2	2	2	2	100			1=Not open yet
32	32	2	1	2	1	102			1=Not open yet
33	38	2	2	2	2	104	Y		1=Not open yet
34	36	2	2	2	2	105			1=Not open yet
35	65	2	2	2	2	105	Y	?	1=Not open yet
36	40	2	3	2	3	106	Y		1=Not open yet
37	39	3	2	2	2	106			1=Not open yet
38	41	2	2	2	2	111			1=Not open yet
39	77	2	2	2	2	113	Y	?	1=Not open yet
40	34	2	2	2	2	114	Y		1=Not open yet
41	44	2	2	2	2	117	Y		1=Not open yet
42	46	2	2	2	2	117		N	1=Not open yet
43	33	2	.	2	.	122	Y	N	2=Open now
44	33	2	.	2	.	122	Y	N	2=Open now
45	33	2	.	2	.	122			2=Open now
46	44	2	2	2	2	124	Y		2=Open now
47	45	2	2	2	2	128			2=Open now
48	85	2	2	2	2	131	Y		2=Open now
49	55	9	2	9	2	134	Y		2=Open now
50	39	2	2	2	2	134			2=Open now
51	44	2	2	2	2	170	Y		3=Closed
52	43	2	2	2	2	181			3=Closed
53	37	2	2	2	2	183	Y		3=Closed
54	94	2	2	2	2	205	Y	N	3=Closed
55	34	2	2	2	2	205	Y	N	3=Closed
56	78	2	2	2	2	219	Y	N	3=Closed
57	35	2	2	2	2	226	Y		3=Closed
58	64	2	2	2	2	228	Y	N	3=Closed
59	36	2	2	2	2	228		N	3=Closed

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Reason for no ROP classification=4=Lowest zone of any vessels is III for one exam

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Plus disease observed	Exam window
60	40	3	2	3	2	57	Y		1=Not open yet
61	38	3	2	3	2	57			1=Not open yet
62	36	3	2	3	2	58			1=Not open yet
63	36	3	2	3	2	59		N	1=Not open yet
64	53	3	2	3	2	60			1=Not open yet
65	37	3	2	3	2	60			1=Not open yet
66	35	3	2	3	2	62			1=Not open yet
67	41	9	3	9	3	64			1=Not open yet
68	36	3	2	3	2	64	Y		1=Not open yet
69	46	3	2	3	2	67			1=Not open yet
70	41	3	2	3	2	68			1=Not open yet
71	37	3	2	3	2	68			1=Not open yet
72	35	3	2	3	2	70	Y		1=Not open yet
73	41	3	2	3	2	73	Y		1=Not open yet
74	40	3	2	3	2	73	Y		1=Not open yet
75	38	3	2	3	2	74			1=Not open yet
76	36	3	2	3	2	76	Y		1=Not open yet
77	37	3	2	3	2	77	Y		1=Not open yet
78	43	3	2	3	2	78			1=Not open yet
79	39	3	2	3	2	78			1=Not open yet
80	38	3	2	3	2	79			1=Not open yet
81	35	3	2	3	2	80			1=Not open yet
82	38	3	2	3	2	81			1=Not open yet
83	39	3	2	3	2	84			1=Not open yet
84	33	3	2	3	2	89			1=Not open yet
85	40	3	2	3	2	89	Y		1=Not open yet
86	34	3	2	3	2	90	Y		1=Not open yet
87	36	3	2	3	2	91			1=Not open yet
88	39	3	2	3	2	91		N	1=Not open yet
89	41	3	2	3	2	93			1=Not open yet
90	34	3	2	3	2	94	Y	?	1=Not open yet
91	37	3	2	3	2	96	Y		1=Not open yet
92	36	3	2	3	2	105			1=Not open yet
93	44	3	2	3	2	115	Y		1=Not open yet

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Data from last ROP exam for infants with missing ROP status who are >=55 weeks PMA

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at 55	FU window
94	44	3	2	3	2	119			2=Open now
95	35	3	2	3	2	124	Y	N	2=Open now
96	37	3	2	3	2	134	Y	N	2=Open now
97	39	3	2	3	2	134			2=Open now
98	46	3	2	3	2	146	Y		3=Closed
99	36	3	2	4	2	147	Y		3=Closed
100	38	3	2	3	2	158	Y	N	3=Closed
101	44	3	2	3	2	201	Y		3=Closed
102	37	3	2	3	2	207	Y	N	3=Closed
103	55	3	2	3	2	208	Y		3=Closed
104	34	3	2	3	3	210		N	3=Closed
105	32	3	P	3	P	212	Y		3=Closed
106	33	3	P	3	P	214	Y		3=Closed
107	36	3	2	3	2	222	Y		3=Closed
108	39	3	2	3	2	222	Y		3=Closed
109	33	3	P	3	P	224	Y		3=Closed
110	34	3	2	3	2	226	Y		3=Closed
111	86	3	2	3	2	226	Y	N	3=Closed
112	39	3	2	3	2	227	Y	N	3=Closed
113	88	3	2	3	2	232	Y	N	3=Closed
114	37	3	2	3	2	236	Y	N	3=Closed

Reason for no ROP classification=5=PMA>=55 weeks but no ROP exams entered

Obs	Estimated PMA on last ROP exam date	Left lowest zone of any vessels	Left lowest zone of any vessels - previous exam	Right lowest zone of any vessels	Right lowest zone of any vessels - previous exam	Current estimated PMA	Acute ROP status lost to FU at 55 weeks PMA	Final ROP status obtained at 55	FU window
115	.	.	.	.	.	55			.
116	.	.	.	.	.	56			.
117	.	.	.	.	.	63			.
118	.	.	.	.	.	65			1=Not open yet

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From: Hensman, Angelita
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Laptook, Abbot
Subject: RE: SUPPORT
Date: Thursday, April 02, 2009 12:44:29 PM

Ok. Will enter it.

Thanks

Angelita

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 02, 2009 12:37 PM
To: Hensman, Angelita; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Laptook, Abbot; Vohr, Betty; Ventura, Suzy
Subject: RE: SUPPORT

Hi Angelita,

Because the NG07 data indicate that infant (b) (6) was on room air by NC at 36 weeks, the PHY01 is actually expected per technical memo SUP14. Any time section C is completed on the NG07, infants enrolled in SUPPORT should have the PHY forms entered in the DMS.

Let me know if you have any questions.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
919-541-8255

From: Hensman, Angelita [mailto:AHensman@WIHRI.org]
Sent: Thursday, April 02, 2009 11:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; Laptook, Abbot; Vohr, Betty; Ventura, Suzy
Subject: RE: SUPPORT

Hi Rose,

(b) (6) - was seen for the 18 month visit in Follow up on (b) (6). We have contacted the ophthalmologist and are awaiting the final results from him.

(b) (6) was born on (b) (6) and per the SUP14 Technical memo does not need the PHY01 form. The NG07 was entered on 3/13/09.

(b) (6) - this family has moved to Indiana. The Indiana site F/U PI and coordinator were e-mailed on 1/20/09 and Vicky also spoke to the coordinator there on 2/3/09. As of this morning no contact had been attempted with the family. Suzy called the Indiana Follow up coordinator again and she was going to get back to her today. We will keep checking.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 4:28 PM
To: Laptook, Abbot; Hensman, Angelita; Vohr, Betty; Ventura, Suzy
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Given the spectacular recruitment from your site, this is amazing!!!!
Thanks
Rose

CENTER	NETWORK	ROP_message
14	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
CENTER	NETWORK	BPD_message
14	(b) (6)	PHY01 is expected based on NG07 but has not been entered.
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: richard.ehrenkranz@yale.edu; elaine.romano@yale.edu; Das, Abhik; Gantz, Marie
Subject: Re: SUPPORT
Date: Wednesday, April 01, 2009 3:41:43 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> We are missing a few SUPPORT outcomes. Let us know how you are doing,
> Thanks
> Rose
>
> | CENTER | NETWORK | ROP_message |
> |---|---|---|
> | 13 | (b) (6) | 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
> | 13 | (b) (6) | 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
>
> | CENTER | NETWORK | FU_message |
> |---|---|---|
> | 13 | (b) (6) | FU marked as complete (per NF10/SF10) but NF09a has not been completed. |
> | 13 | (b) (6) | FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed. |
> | 13 | (b) (6) | FU marked as complete (per NF10/SF10) but NF09a has not been completed. |
>
> Rosemary D. Higgins, MD
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
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> Bethesda, MD 20892
> For overnight delivery use Rockville, MD 20592
> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Hi Rose,
We were able to obtain additional outpatient eye exam results on 7533 1 and now final status was reached with 2 consecutive eye exams in zone 3 with stage 3 regressed ou. We are still trying to contact 7530 1 who was transferred to another hospital and was not scheduled to return for followup exam until 8-12 months old. thanks,
Monica

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Bridge, Renee
Cc: Rich, Wade; Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Wednesday, April 01, 2009 11:00:25 AM

Jenny and I looked into this, and it turns out that NF forms were entered for the infants instead of SF forms (intended for SUPPORT infants not in GDB). Jenny will contact UCSD to resolve that issue, but it does look like we have the data.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 31, 2009 4:42 PM
To: Bridge, Renee; Gantz, Marie
Cc: Rich, Wade
Subject: RE: SUPPORT

Marie-
Do we have the data on the missing forms listed below??
Thanks
Rose

-----Original Message-----
From: Bridge, Renee [mailto:rbridge@ucsd.edu]
Sent: Tuesday, March 31, 2009 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: SUPPORT

Dear Dr. Higgins, I am working on (b) (6), but I checked the data entry for (b) (6) and the missing forms are complete. Please let me know if you have other information. I am starting to go through each file to assess for missing info. Thank you. Renee Bridge, RN UCSD Neonatology

---

From: Rich, Wade
Sent: Monday, March 30, 2009 2:02 PM
To: Bridge, Renee

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Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 1:44 PM
To: Finer, Neil; Rich, Wade; Vaucher, Yvonne; Fuller, Martha
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Thanks
Rose
CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

22

(b) (6)

No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

CENTER

NETWORK

FU_message

22

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

22

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch

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From: Finer, Neil
To: "Kennedy, Kathleen A"; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT and retinopathy
Date: Tuesday, March 31, 2009 4:30:35 PM

I am supportive but would like to see answers to Kathleen's questions.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, March 31, 2009 1:16 PM
To: Phelps, Dale; higginsr@mail.nih.gov
Cc: Finer, Neil
Subject: RE: SUPPORT and retinopathy

I wrote a brief proposal for this in Oct 2007 after Dale and I discussed it (attached). I really thought it needed some input from an ophthalmologist (see questions in red) so I sent it Helen Hittner (our ophthalmologist). She had initially expressed interest and then never responded (got busy with the Avastin study). I also got the impression that Dale wasn't very interested so I let it drop. I'd be happy to pick it up and do most of the work if Dale and Neil are interested. Maybe Dale could answer the questions that I posed to Helen in the attachement.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, March 30, 2009 12:40 PM
To: higginsr@mail.nih.gov; Kennedy, Kathleen A
Cc: nfiner@ucsd.edu
Subject: Re: SUPPORT and retinopathy

I remain very interested in this. However I can not work on it until INS-2 is launched.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Kathleen.A.Kennedy@uth.tmc.edu ; Phelps, Dale
Cc: nfiner@ucsd.edu
Sent: Mon Mar 30 11:58:07 2009

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Subject: SUPPORT and retinopathy

Dale and Kathleen

The SUPPORT subcommittee met today to discuss data analysis. I recall that there was some discussion with the two of you regarding a "natural history" analysis of the ROP exams. Let me know if there is still interest in this as we had not received any secondary proposal to perform this analysis.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Kennedy, Kathleen A
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: nfiner@ucsd.edu
Subject: RE: SUPPORT and retinopathy
Date: Tuesday, March 31, 2009 4:15:54 PM
Attachments: ROP Natural History Study.doc

I wrote a brief proposal for this in Oct 2007 after Dale and I discussed it (attached). I really thought it needed some input from an ophthalmologist (see questions in red) so I sent it Helen Hittner (our ophthalmologist). She had initially expressed interest and then never responded (got busy with the Avastin study). I also got the impression that Dale wasn't very interested so I let it drop. I'd be happy to pick it up and do most of the work if Dale and Neil are interested. Maybe Dale could answer the questions that I posed to Helen in the attachement.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, March 30, 2009 12:40 PM
To: higginsr@mail.nih.gov; Kennedy, Kathleen A
Cc: nfiner@ucsd.edu
Subject: Re: SUPPORT and retinopathy

I remain very interested in this. However I can not work on it until INS-2 is launched.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Kathleen.A.Kennedy@uth.tmc.edu ; Phelps, Dale
Cc: nfiner@ucsd.edu
Sent: Mon Mar 30 11:58:07 2009
Subject: SUPPORT and retinopathy

Dale and Kathleen

The SUPPORT subcommittee met today to discuss data analysis. I recall that there was some discussion with the two of you regarding a "natural history" analysis of the ROP exams. Let me know if there is still interest in this as we had not received any secondary proposal to perform this analysis.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Retinopathy of Prematurity (ROP) Natural History Study
Secondary Study for SUPPORT Trial

Kathleen A, Kennedy, MD, MPH and Helen Mintz-Hittner, MD

Introduction and Rationale

Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines[1] are based on natural history data from the CRYO-ROP[2] and LIGHT-ROP[3] studies. The CRYO-ROP study[4] remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, although it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.[5] Over the past two decades, survival of lower gestational age infants has increased.[6] For infants 501-1000 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002. The timing of onset of ROP is related to both gestational age and postnatal age. The impact of increased survival on the incidence and timing of onset of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "old threshold"). Based on the results of ET-ROP study, earlier treatment (now termed "new threshold") is now recommended.[7] In the ET-ROP study, 60% of the infants with pre-threshold ROP (by the conventional definition used in the CRYO-ROP study) met the high-risk pre-threshold criteria for this earlier "new threshold" treatment. Based on these new treatment criteria, screening must now be initiated early enough to reliably identify infants with high-risk pre-threshold, rather than "old threshold", ROP. In the CRYO-ROP study, for infants <750 g, ROP (any severity) occurred in 90% and reached pre-threshold in 39%. In 750-999 g infants ROP occurred in 78% and reached pre-threshold in 21%. In the <750 g infants, less than 5% of infants who reached pre-threshold ROP did so by 32.3 weeks postmenstrual age; in 750-999 g infants, <5% of those who reached pre-threshold ROP did so by 32.6 weeks postmenstrual age. In this study, <1% of infants who reached pre-threshold ROP did so by 30.9 weeks postmenstrual age.

In addition to information about when screening must begin, clinicians need information about when the baby is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who have been discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the threshold ROP criteria had done so by 45.9 weeks postmenstrual age. Helen, can we assume that treatment initiated after this would not be beneficial? It seems to me that there must be some window after this during which treatment is worth considering. We're mainly talking about babies who were lost to follow-up so you don't know what happened in the interim, but you want to stop looking for them.

In the NICHD Network SUPPORT trial, severe ROP (threshold or need for surgery) is the primary outcome for the O_2 saturation target arm of the factorial design. For this study, extensive ROP outcome data, in addition to the ROP outcome data routinely collected for the GDB, is being prospectively collected for all enrolled infants. Infants 24 0/7 – 26 6/7 weeks gestation are eligible for this study. A sample size of 1310 infants is planned. For enrolled infants who survive until the first eye exam, the following data are recorded at each eye exam: the date of the eye exam, the highest stage and lowest zone of ROP, whether the infant met the criteria for "new threshold" ROP using the new ET-ROP definition, and whether treatment was administered. Examinations are continued according to current non-study screening recommendations: until either vascularization has reached zone 3, the infants is 45 weeks postmenstrual age without prethreshold ROP, or ROP has regressed. These data will allow us to track the distribution of postnatal age and postmenstrual age at which treatable ROP occurs, using the new criteria for treatment and current survival demographics. Helen, do you think it's worth the effort if we're not going to have any data on babies < 24 weeks?

We will use the data collected for this trial to generate tables and possibly figures, similar to those published from the CRYO-ROP and ET-ROP studies[3], illustrating the distribution (with 1%, 5%, median, 95% and 99%iles) for the onset of ROP that meets the new threshold criteria for treatment.

Methods

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Postmenstrual age will be calculated as gestational age at birth in weeks + days, using the Best Obstetrical estimate, plus the postnatal age in days at the time of exam. In cases where the findings differ between eyes, the age of onset will be recorded as the age at which the diagnostic criteria were met in the first eye. In the 2002 CRYO-ROP/LIGHT-ROP paper, the authors included the timing for onset in the second eye as well as the first eye that developed each criterion. Do you think that's necessary? It seems like it would be simpler to just record the time of onset for the first eye that met the criteria.

Analytic Plan

A Baseline Characteristics Table will include the following summary statistics for all enrolled infants and for infants who survived until the first eye exam: birth weight (mean, SD), gestational age (mean, SD), race (% by category), sex (% by category), multiple birth (% by category)

The following Outcome Table will be generated:

		Postmenstrual Age (weeks)					Postnatal Age (weeks)				
ROP	n	1%	5%	Median	95%	99%	1%	5%	Median	95%	99%
Prethreshold											
New Threshold											

Separate tables will be generated for each of the trial strata (24 – 25 6/7 weeks and 26 – 26 6/7 weeks). If the data are indistinguishable, they will be combined and reported in a single table.

Limitations

We cannot generate incidence data because only consented inborn infants are included. The inclusion criteria will not allow us to generalize to infants < 24 weeks gestation. (NG03 form from the GDB does not include any dates of onset.)

We need to find out how much of a problem we have with missing data.

A potential criticism is the lack of certified ROP examiners.

---

[1] Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 117: 572-6, 2006. Erratum (screen gestational age of 30 weeks or less) in: Pediatrics 118: 1324, 2006.

[2] Palmer EA et al. Incidence and early course of retinopathy of prematurity. Ophthalmology 98: 1628-1640, 1991.

[3] Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 120: 1470-6, 2002.

[4] Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. Pediatrics 81: 697-706, 1988 and Arch Ophthalmol 106: 471-479, 1988.

[5] Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. N Engl J Med 338: 1572-6, 1998.

[6] Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Ob Gynecol 196(2):147 e1-8, 2007.

[7] Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 102: 233-250, 2004.

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu; "nancy newman"; drfjcmd@aol.com
Subject: RE: SUPPORT
Date: Tuesday, March 31, 2009 9:22:23 AM

We have been pursuing this mother, and she has been reported. We have the baby scheduled for ophthalmology f/u on (b) (6)
Bonnie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 4:26 PM
To: mcw3@cwru.edu; nancy newman; bss5@cwru.edu; (b) (6)
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Given the spectacular recruitment from your site, this is amazing!!!!
Thanks
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Michael Cotten; gloria.siaw@duke.edu; Ronald N Goldberg; Gantz, Marie
Subject: Re: SUPPORT
Date: Monday, March 30, 2009 5:15:22 PM

Rose
Please see the responses below for each subject requested.

(b) (6) This child was lost to follow up per provider - missed 2 appts and letters sent out with no response. This information has been logged into the database.
(b) (6) This child has been seen here at Duke and we are waiting on response from the eye center to put it into the database.
(b) (6) This child has data reported for 55 weeks and we are trying to track down the 18 month information.
(b) (6) ROP has resolved. Information in NRN database.
(b) (6) This child has not had any follow up at Duke other than the 18 month visit. We are trying to track down the information from the parent.

Sorry for the delay.
Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-(b)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

03/30/2009 04:41 PM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Kimberley A Fisher" <kimberley.fisher@duke.edu>, <gloria.siaw@duke.edu>
cc "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,
Thanks
Rose

CENTER NETWORK ROP_message

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19	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported. This child was lost to follow up per provider - missed 2 appts and letters sent out with no response. This information has been logged into the database.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
19		The patient is within their Fol-up window and final ROP status has not been reported.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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From: Wally Carlo, M.D.
To: Finer, Neil; Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: GA of SUPPORT infants
Date: Monday, March 30, 2009 4:47:42 PM

GREAT!

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, March 30, 2009 2:57 PM
To: Rich, Wade; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: GA of SUPPORT infants

FYI
This looks good we have a significant number of infants < 26 weeks = 564 – This is great and the groups are nicely balanced
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, March 30, 2009 11:48 AM
To: Finer, Neil
Subject: GA of SUPPORT infants

Neil,

Attached are frequencies of the GA of the SUPPORT infants, by treatment. Note that there are 8 infants whose NG02 has not yet been entered, thus GA is not yet known.

I will get you information regarding infants with missing primary outcomes later this week.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, March 30, 2009 4:39:21 PM

Rose:

I really appreciate your recognition of our RNs' great performance. I know they try hard to perform well.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 30, 2009 3:30 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Shirley Cosby; Monica Collins; Vivien Phillips
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. Let us know how you are doing,

Given the spectacular recruitment from your site, this is amazing!!!!

Thanks

Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Finer, Neil
To: Rich, Wade; "Wally Carlo, M.D."
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: GA of SUPPORT infants
Date: Monday, March 30, 2009 3:57:12 PM
Attachments: SUPPORT infants by GA and treatment 03-30-09.rtf

---

FYI
This looks good we have a significant number of infants < 26 weeks = 564 – This is great and the groups are nicely balanced
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, March 30, 2009 11:48 AM
To: Finer, Neil
Subject: GA of SUPPORT infants

Neil,

Attached are frequencies of the GA of the SUPPORT infants, by treatment. Note that there are 8 infants whose NG02 has not yet been entered, thus GA is not yet known.

I will get you information regarding infants with missing primary outcomes later this week.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Infants enrolled in SUPPORT by treatment and GA

The FREQ Procedure

Table of OBGGAWKS by cpap			
OBGGAWKS(Gestational Age (weeks))	cpap(Ventilation arm)		
Frequency Col Pct	CPAP	Surfactant	Total
23	1 0.15	1 0.15	2
24	109 16.49	112 17.28	221
25	175 26.48	168 25.93	343
26	167 25.26	170 26.23	337
27	209 31.62	195 30.09	404
28	0 0.00	2 0.31	2
Total	661	648	1309
Frequency Missing = 8			

Table of OBGGAWKS by oximeter			
OBGGAWKS(Gestational Age (weeks))	oximeter(Oxygenation arm)		
Frequency Col Pct	High O2	Low O2	Total
23	0 0.00	2 0.31	2
24	112 17.05	109 16.72	221
25	175 26.64	168 25.77	343
26	166 25.27	171 26.23	337
27	203 30.90	201 30.83	404
28	1 0.15	1 0.15	2
Total	657	652	1309
Frequency Missing = 8			

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From: Laptook, Abbot
To: Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT subcommittee Call
Date: Monday, March 30, 2009 12:45:59 PM

Sorry, on service and just couldn't get to this call. AL

From: Cunningham, Meg [mcunningham@rti.org]
Sent: Monday, March 30, 2009 9:16 AM
To: Webb, Robin E.; Laptook, Abbot; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu; Poole, W. Kenneth; mcw3@cwru.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Vecchio, Brenda; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Carolyn.Grier@UHhospitals.org
Subject: RE: SUPPORT subcommittee Call

Reminder for today's call.

From: Webb, Robin E.
Sent: Tuesday, March 10, 2009 3:42 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; Poole, W. Kenneth; 'mcw3@cwru.edu'
Cc: '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Carolyn.Grier@UHhospitals.org'
Subject: SUPPORT subcommittee Call

The call to discuss plans for data analysis and mock tables has been scheduled for:

Monday, 3/30
11:00am ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
[redacted]#

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From:	Cunningham, Meg
To:	Webb, Robin E.; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu; Poole, W. Kenneth; mcw3@cwru.edu
Cc:	sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Carolyn.Grier@UHhospitals.org
Subject:	RE: SUPPORT subcommittee Call
Date:	Monday, March 30, 2009 9:16:47 AM
Attachments:	SUPPORT_Call_03302009.doc

Reminder for today's call.

From: Webb, Robin E.
Sent: Tuesday, March 10, 2009 3:42 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; Poole, W. Kenneth; 'mcw3@cwru.edu'
Cc: '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Carolyn.Grier@UHhospitals.org'
Subject: SUPPORT subcommittee Call

The call to discuss plans for data analysis and mock tables has been scheduled for:

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Then, enter Participant Passcode:
(b) (6)

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8.1.1 Analysis Plan

The primary analyses of this factorial trial will be a logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO2) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

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Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%)†					
Cerebral palsy at 18-22 months (%)†					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%)†					

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Unilateral blindness at 18-22 months (%)†					
Deafness at 18-22 months†					

†Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥2 (%)				
PDA requiring surgery				

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From: Cunningham, Meg
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT subcommittee Call
Date: Friday, March 27, 2009 2:41:52 PM

Hi Dr. Finer,

Do you have any materials you would like me to distribute before Monday's call?

Meg

From: Webb, Robin E.
Sent: Tuesday, March 10, 2009 3:42 PM
To: Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; Poole, W. Kenneth; 'mcw3@cwru.edu'
Cc: '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; 'msumner@peds.uab.edu'; Zaterka-Baxter, Kristin; 'Carolyn.Grier@UHhospitals.org'
Subject: SUPPORT subcommittee Call

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Monday, 3/30
11:00am ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: <kzaterka@rti.org>; <ericav@stanford.edu>
Subject: Re: SUPPORT MRI"s
Date: Friday, March 27, 2009 10:26:39 AM

Rose
Pat is not yet convinced that he needs or could schedule an on site central read. I plan to sit with him for the first several MRI with the new forms (when they are ready). Perhaps I can convince him then.

Susan

Sent from my iPhone

On Mar 27, 2009, at 4:55 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov > wrote:

> Do we have a potential date(s) for central reading? There is a
> reasonable chance that I can attend for at least one of the days.
>
> Rose
> Rosemary D. Higgins, MD
> Program Scientist
> NICHD
>
> ----- Original Message -----
> From: Susan Hintz <srhintz@stanford.edu>
> To: kristin zaterka <kzaterka@rti.org>
> Cc: erica <ericav@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Thu Mar 26 19:40:31 2009
> Subject: SUPPORT MRI's
>
> Hi Kris,
>
> We have gotten back all of the MRI's that Dr. Barnes had in his
> possession - so, they are coming BACK to you to re-check in as if
> they were NEVER READ (and in most cases, they were not yet read).
> Even the MRi's that are in envelopes and labeled should be considered
> NOT read because of the form change. They all need to be
> re-enveloped and the new and improved central reader form.
>
> By the way - have you guys started to make the changes to the central
> reader form so we can "bless it" with Dr. Barnes before you start
> copying and stuffing envelopes? I know you were in training until
> recently. I sent the central reader form changes to you and others
> on 3/17 by email. Did you get it?
>
> Thanks -
>
> Susan
> --
> Susan R. Hintz, M.D., M.S. Epi
> Associate Professor of Pediatrics
> Division of Neonatal and Developmental Medicine

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> Stanford University School of Medicine
> 750 Welch Road, Suite 315
> Palo Alto, CA 94304
> ph: 650-723-5711
> fax: 650-725-8351
>

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Thursday, March 26, 2009 1:02:24 PM
Attachments: Infants with missing outcomes 03-26-09.xls

Rose,

Attached is the list of infants who are missing SUPPORT outcomes. I will run the report again in two weeks.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
12		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
12		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient's follow-up window has closed and final ROP status has not been reported.

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19	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
19		The patient is within their Fol-up window and final ROP status has not been reported.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.

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From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: SUPPORT Cost study
Date: Friday, March 20, 2009 9:13:30 AM
Attachments: SUPPORT secondary proposal.doc

Hi Rose and Neil,
Attached is a study for consideration by the SUPPORT Subcommittee to look at incremental costs in respiratory care in the SUPPORT cohort.
Thanks for your consideration!
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
USA
TEL: 513-862-3007
PAGER: 513-736-(b)
E-mail: kurt.schibler@cchmc.org

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

The Business Case for Cost Effective Respiratory Management in the NICU (SUPPORT-Secondary Study)

Investigators: Vivek Narendran MD, MBA and Kurt Schibler MD

Background: Concern about high and rising health care costs in the United States has increased sharply in recent years. President Obama has made health care a priority, with a particular interest to decreasing costs and believes that it is no longer just a moral imperative, but a fiscal imperative to address this issue. Currently, the US health care spending is 16% of GDP and is projected to increase to 19.5% by 2017. In 2007, the US spent $ 2.26 trillion on health care or $ 7,439 per person up from $2.1 trillion or $ 7026 per capita, the previous year. *Technology,* not demographics or medical malpractice is the key driver of health care spending, accounting for an estimated half to two thirds of spending growth. Decision regarding respiratory support strategy is among the most critical choice impacting total cost for an ELBW in the NICU.

In this study, we propose to determine the incremental financial impact of different respiratory care practices in managing extremely low birth weight preterm infants. This retrospective study will include all patients enrolled in the NICHD neonatal network sponsored SUPPORT trial. By using this randomized cohort of infants, we intend to quantify the cost of different interventions and the financial impact resulting from preventing intubation and mechanical ventilation from multiple stakeholder perspectives, including third party payers. The data sources are the existing SUPPORT database and cost of care database of all the participating hospitals. The cost of care for all eligible infants from NICU admission to discharge home, death or 120 days of age (which ever occurs first) will be used to estimate average costs of infants on different respiratory strategies. We will facilitate collection of this data by collaborating with site PI's and financial analysts at different hospitals.

Primary Hypothesis:

1. We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU *will result in decreased costs with similar outcomes.*
2. We hypothesize that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) *will result in decreased costs with similar outcomes.*

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From:	Susan Hintz
To:	kristin zaterka
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; petrie@rti.org; adas@rti.org; mcunningham@rti.org; mbball@stanford.edu; vanmeurs@stanford.edu
Subject:	MRI central reader form changes
Date:	Tuesday, March 17, 2009 6:33:48 PM
Attachments:	ChangesSUPPORTMRIcentral031609.doc

Hi all,

Dr. Barnes and I had a lengthy meeting yesterday to revise and finalize the SUPPORT MRI central reading form. The main issues are to make this a better, more complete document, and to create a form in which there is no temptation for written comments or extra marks, which would be impossible for the data entry folks to interpret. Some of the changes involve moving modified sections from the Hypothermia MRI form to the SUPPORT form, but others are based on Dr. Barnes' concerns about lack of clarity and quantitative measures in some areas of the Hypothermia forms.

Dr. Barnes knows that these changes mean he WILL NEED TO re-read the MRI's for SUPPORT already read. He also understands the time crunch - i.e., must be completed with time for data entry and analysis for the PAS 2010 late breaker abstract deadline. (I estimated that he needed to be completely done with the readings by August 2009 - that might be too fast, but rather an early than late deadline)

Attached are the changes. There will be another document to follow with changes to the KEY.

Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi
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Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
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Changes to SUPPORT MRI central reading form
March 16, 2009 Hintz

1) Section A: Identification

Please replace SUPPORT Section A with the Hypothermia Section A, but with the following change: A.4 should be "PMA in weeks and days at time of MRI". Dr. Barnes does not fill that in, but I assume that RTI will have an easy calculator for this question.

2) Section B: Signal Abnormalities

After the GRE column, please add a column for "DWI" and a column for "ADC"

3) Section C:

Section C.1.a – Gray matter maturation - This is OK – no changes needed
Section C.1.b – **Please replace this section with the following, which has been modified from Hypothermia section C.1.c:**

C.1.b Subarachnoid space: Measure space as indicated in millmeters, then assess space qualitatively *(normal, mild-moderate enlargement, marked enlargement).* NE=not evaluable

	Measure in mm	Normal	Mild-mod enlargement	Marked enlargement	NE
C.1.b.1 LEFT convexity	_ _ _ _				
C.1.b.2 RIGHT convexity	_ _ _ _				
C.1.b.3 ANTERIOR interhemispheric	_ _ _ _				
C.1.b.4 POSTERIOR interhemispheric	_ _ _ _				

Section C.2.a White matter maturation – this is OK – no changes needed

Section C.2.b – **Please replace this section with the following, which has been modified from Hypothermia section C.2.d and C.2.e**

C.2.b Corpus callosum regions. Measure indicated region of CC in millimeters (sagittal view), then assess thinness of region qualitatively (*normal, equivocal, marked).* NE=not evaluable

	Measure in mm	Normal	Mild-moderate	Marked	NE
C.2.b.1: genu	_ _ _ _				
C.2.b.2: body	_ _ _ _				
C.2.b.3: splenium	_ _ _ _				

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March 16, 2009 Hintz

C.2.c QUALITATIVE assessment of overall corpus callosum thinness (check one box only)

	Normal	Mild	Moderate	Marked	NE
Overall CC					

Section C.2.c and C.2.d – **Please remove these sections and replace with the following, modified from Hypothermia sections C.2.g, C.2.f, and C.2.h:**

C.2.c. Lateral ventricle measurements. Measure indicated areas in millimeters

	LEFT	RIGHT
C.2.c.1 Frontal **horn** of lateral ventricle	____ mm	____ mm
C.2.c.2 Frontal **lobe**	____ mm	____ mm
C.2.c.3 Midbody of lateral ventricle	____ mm	____ mm
C.2.c.4 Midcerebrum	____ mm	____ mm
C.2.c.5 Trigone	____ mm	____ mm
C.2.c.6 Temporo-occipital lobe at trigone	____ mm	____ mm

C.2.d. QUALITATIVE assessment of lateral ventricular dilation (Check one only)

	Normal	Mild	Moderate	Marked	Shunted
C.2.d.1 LEFT					
C.2.d.2 RIGHT					

C.2.e Third and fourth ventricle, temporal and occipital horn and lobe measurements. Measure indicated region in millimeters. Then, assess QUALITATIVELY level of enlargement of VENTRICLE or HORN, if any, as indicated (check only one box).

	Measurement	Normal	Mild-moderate	Marked dilation	NE
Third ventricle					
C.2.e.1 (width)	___ mm				
Fourth ventricle					
C.2.e.2 (width)	___ mm				
C.2.e.3 (AP)	___ mm				
Temporal horn					
C.2.e.4 (LEFT)	___ mm				
C.2.e.5 (RIGHT)	___ mm				
Temporal lobe					
C.2.e.6 (LEFT)	___ mm				
C.2.e.7 (RIGHT)	___ mm				
Mid-occipital horn (width)					
C.2.e.8 (LEFT)	___ mm				
C.2.e.9 (RIGHT)	___ mm				
Temporo-occipital lobe					

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Changes to SUPPORT MRI central reading form
March 16, 2009 Hintz

(width) at occipital					
C.2.e.10 (LEFT)	___ mm	[redacted]			
C.2.e.11 (RIGHT)	___ mm				

Section D. Intraventricular content – this section OK – no changes

Section E. Other – **Please remove this section and replace with the following** (which more closely relates to the end section of the CUS central reading form)

E. Other

	LEFT		RIGHT	
	Yes	No	Yes	No
Structural abnormalities				
If yes, comments:				

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT awards
Date: Tuesday, March 17, 2009 12:38:15 PM
Attachments: SUPPORT center awards for Rose 3-17-09.doc

Rose,

Attached is a list of potential award ideas for the centers we discussed. Let me know if you want me to keep digging.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Potential awards for SUPPORT centers
MG 3-17-09

Wayne State

- Most improved enrollment. Site visit was in December 2006. Through December had enrolled 8 infants. From January 2007 to the present they enrolled 60 infants (88% of their total enrollment). The only centers that enrolled more during that time period were UAB and Brown.

Cincinnati

- Of the sites who recruited throughout the entire study, had the highest rate of multiples (32% of infants enrolled). 4th highest enroller overall. (Most efficient recruiter?)
- One of the lowest rates of protocol deviations at 10% of enrolled infants. Second only to UCSD who had 7%.

Houston

- 6th biggest recruiter overall, but did it the hard way, enrolling 80% singleton babies (highest rate of singletons among top enrollers, 3rd highest rate over all centers).

Emory

- 4th highest enrollment.
- No nasal breakdown reported (along with 8 other centers).

Duke

- 2nd highest rate of enrolling singletons with 83% (Dallas had 84%). 11th highest enrollment overall.
- 2nd highest rate of enrolling infants who were 24 weeks GA with 26% (Wayne State had 28%).
- No chest compressions reported.
- No nasal breakdown reported.

Utah

- 100% of BPD outcomes reported for infants who survived to 36 weeks (along with UNM, Wayne State and Dallas)

UNM

- 100% of BPD outcomes reported for infants who survived to 36 weeks.
- Most persistent: from Antenatal study, highest average number of attempts to obtain a consent (mean 3.5).
- Lowest overall rate of adverse events (33%).

3 Sites have 100% of ROP outcomes reported for survivors to 55 weeks PMA:

- Dallas
- Stanford
- Tufts

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From: Bancalari, Eduardo
To: Raju, Tonse (NIH/NICHD) [E]; ebancalari@miami.edu; nclaure@miami.edu; keszlerm@georgetown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised: Part A: Manuscript--Respiratory
Date: Tuesday, March 17, 2009 11:19:53 AM
Attachments: PART A PULMONARY CARE REVISED 3 17 09.doc

Hi Tonse, attached is the draft with some suggestions from Nelson and me.
Best, Eduardo

Eduardo Bancalari
Professor of Pediatrics
Director Division of Neonatology

-----Original Message-----
From: Raju, Tonse (NIH/NICHD) [E] [mailto:rajut@mail.nih.gov]
Sent: Monday, March 16, 2009 9:52 AM
To: Raju, Tonse (NIH/NICHD) [E]; ebancalari@miami.edu; nclaure@miami.edu; keszlerm@georgetown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Revised: Part A: Manuscript--Respiratory

Hi, Eduardo, Nelson and Marty.

Please use this version--delete the one I sent yesterday, which had too many errors.

Thanks.

Tonse N. K. Raju, MD, DCH
Program Scientist/Medical Officer
Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
6100 Executive Blvd, Bethesda, MD 20892-MS7510 (For FedEx etc., Rockville, MD 20852)
phone: 301-402-1872, Fax: 301-496-3790
e-mail. rajut@mail.nih.gov

-----Original Message-----
From: Raju, Tonse (NIH/NICHD) [E]
Sent: Sunday, March 15, 2009 5:41 PM
To: 'ebancalari@miami.edu'; 'nclaure@miami.edu'; 'keszlerm@georgetown.edu'
Subject: Part A: Manuscript--Respiratory

Hi Eduardo, Nelson, and Marty,

The attached segment of the devices workshop manuscript deals with respiratory section. Please look over and feel free to edit and make suggestions. We may need to further cut down its length, because with four more themes to go, if this length becomes the average, the

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manuscript would be prohibitively lengthy. A quick turn around would be greatly appreiciated.

There is only two pages of text and one table.

With warm regards

Tonse

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Developing Safe and Effective Instruments and Devices for Use in the Neonatal Intensive Care Units: A Workshop Summary

Abstract

In February 2009, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) invited a team of experts to address the issues concerning the development of safe and effective instruments and devices for use in the neonatal intensive care units (NICU). Five topic areas were the focus of the discussions: 1) respiratory; 2) cardiovascular; 3) cerebrovascular; 4) metabolic; and 5) infections. Clinical needs, the status of current device/product technologies and their limitations, and future research opportunities were the crosscutting themes across topics. This paper provides a brief summary of the proceedings.

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Neonatal Pulmonary Care

Delivery Room Equipment: Considering the wide range of medical and surgical conditions encountered during resuscitation of high-risk infants, it is surprising that much of the equipment being used in the delivery room has remained outdated. Some examples of emergencies requiring resuscitation in the delivery room include: preterm infants with immature lungs; meconium aspiration syndrome and persistent pulmonary hypertension; perinatal asphyxia; congenital diaphragmatic hernia; abdominal wall defects; and anomalies of the upper airways. Some immediate needs are: blenders to fine-tune administered oxygen concentration during resuscitation, ability to monitor pressure generated and tidal volumes delivered while providing intermittent positive air pressure ventilation (IPPV) or continuous positive airway pressure (CPAP); and devices to assess the adequacy of gas exchange ~~immediately after birth~~immediately after birth.

Assisted ventilation and oxygen supplementation, during transportation and in the NICU: Major advances in ventilatory support techniques and exogenous surfactant therapy in past two decades have led to marked increase in survival rates, especially for very low birth weight infants (VLBW, <1500 grams at birth). However, in contrast to older children and adults with lung diseases, most VLBW infants require ventilatory support for prolonged durations. ~~In one study, 80% of infants with birth weight <700 grams, and 50% with birth weights 700-1500 grams still required assisted ventilation on the 28th day.~~ Prolonged duration of assisted ventilation and supplemental oxygen markedly increases the risk for bronchopulmonary dysplasia (BPD) and Retinopathy of Prematurity (ROP). Depending upon the definition, the reported incidence of BPD in infants <1000 grams ranges between 44% to 75%. Since over 85% of such infants in this birth weight survive, a substantial number of infants and children will add to the pool of adults with pulmonary disability. ~~These infants also spend considerable periods of time above the intended ranges of arterial oxygen saturation which further increases the risk for BPD and retinopathy of prematurity.~~

The above data underscore the major clinical need for improving the quality of ventilatory support, with intent to reduce the duration of required assisted ventilatory support and to minimize ongoing lung injury. Such efforts require ~~more gentle~~gentler and less invasive modalities for respiratory support. Efforts need to begin by improving devices used in the delivery room resuscitation, and during transportation, since even a brief period of inappropriate ventilatory assistance can ~~cause~~ set a stage for ~~ongoing~~ progressive lung damage in premature infants.

In recent years, a number of new respiratory devices have been introduced for neonatal use; these are patient-triggered ventilators, in which synchronization results in larger tidal volumes with lower airway pressures. The limitations of these systems include, low sensitivity to trigger; delay in initiating a trigger breath; excessive sensitivity to artifacts (leaks or condensation of water in circuit); termination of inspiration too early causing insufficient tidal volume; initiating the trigger too late leading to extended

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~~expiration~~inspiration; flow sensors adding dead space increasing CO2 retention. In addition, leaks around the endotracheal tube can cause auto cycling ~~poor~~ and poor estimation of tidal volume, with larger ~~delivery of~~ ventilator-delivered tidal volume compared the patient ~~delivered~~ tidal volume.

There is a variety of high frequency ventilatory (HFV) equipment, and their relative merits and limitations remain to be tested. ~~Besides such studies~~ In addition, HFV equipment for use during infant transport needs to be developed.

Among other newer modes of ventilatory systems are, non-invasive ventilation~~or~~ (NIMV); nasal continuous positive airway pressure (N-CPAP); and ~~the~~ neurally adjusted ventilatory assist (NAVA). ~~The~~ NAVA uses electrical signal from diaphragm via esophageal electrodes; much work needs to be done to assess the efficacy and safety of this ventilation modality.~~bring these devices to the market.~~

Some elements of an ideal ~~respirator~~ ventilator would be that it responds to changing physiological needs by automatic fine-tuning, rather than only when the caregiver pays attention to the patient. Such devices will assure that the patient spends more time at the ~~target~~ intended range of ventilation and arterial blood gases;. ~~with little if any time spent beyond the target range.~~ The ultimate goal ~~of developing~~ is the development of devices that will drastically reduce or eliminate chronic lung damage because of artificial ventilation, by reducing both the duration and extent of ventilatory support, and overcoming currently recognized deficiencies in ventilatory support systems.

Pulmonary Function Assessment: Currently available methods for assessing pulmonary function in the newborn infants include: chest radiograph; CT scan; respiratory induced plethysmography (RIP); helium dilution and nitrogen washout methods; body plelthysmograph; blood gas/acid base analyses as a proxy for adequacy of ventilation perfusion match and gas exchange. Each of the above method has limitations, and none is able to provide continuous information concerning changing pulmonary function status in sick newborn infants being treated with assisted ventilatory support. Thus, one of the most urgently felt needs by clinicians is the wide availability of simple bedside tools and methods for providing such vital information as adequacy of alveolar inflation, appropriateness of ventilation/perfusion match, and measures of barotraumas.

Other Aspects of Pulmonary Care: The endotracheal (ET) tube technology has not improved in over 20 years. This problem is acutely apparent while treating extremely small preterm infants whose tracheal internal diameter is often equal to the size of the smallest available ET tube. Their thick walls and small lumen lead to high resistance, and even minimal blockage due to respiratory secretions can lead to major reductions in flow volumes. While ET tubes without external cuff are used to avoid potential pressure injury to the trachea, with the advanced material bioengineering, it should be possible to produce pliable, but stiffer, ET tubes with thinner walls, allowing for enhanced internal diameter. Potential for developing leak-proof cuffs at least for use on an intermitted basis to assess pulmonary function would be valuable.

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Ideal ET tubes may be considered to have the following characteristics: thinner walls to maximize luminal diameter; of sufficient rigidity to pass it through the glottis; with soft tips to avoid damage to the airways; visible on chest x-rays; with soft cuffs (intermittently inflatable) to minimize leaks; integrated CO2 detectors to help assess tube dislodgement; and with fiber optic lights at the end of the tube to visualize tube location without x-rays.

Collaboration and Education: It would be very beneficial for the device manufacturers to consult neonatologists and pulmonary experts input prior to prototype development on matters of clinical needs as well as design and compatibility of such products. Additional benefits could be gained by promoting trials to assess effects of new and existing devices and strategies on outcome. Academic societies may need to consider developing standard nomenclature for ventilator modalities, and education of personnel about use of the existing and new equipment.

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Table I: New and Improved Devices/Equipment for use in Neonatal Respiratory Care

Area	Shortcomings and Needed Improvements
Resuscitation Equipment in the Delivery Room	• Generic devices: More efficient devices ~~providing~~ to provide CPAP (e.g., valves and bubbles); IPPV (self-inflating, flow inflating, interrupters, and T-Piece) need optimizing to meet specific types of ventilatory needs in the delivery room. • Gas Exchange: devices to assess adequacy of oxygenation and CO_2 elimination • Simple devices to monitor inspiratory and end-tidal pressures, delivered tidal volumes ~~or~~ and FRC • Improved air-oxygen blender set up in all delivery rooms to allow use of ~~FIO_2~~ FiO_2 at < 100% concentrations • Improving and standardizing all DR equipment in design and functionality
Respiratory support in the during transportation and in the NICU **Ventilators**	• *Patient-triggered ventilators*: avoiding leaks and other artifacts to prevent auto trigger at excessive ventilator rates; improving sensitivity and avoiding trigger delay and uncoordinated ventilator-to-patient cycle; and minimizing dead space. • *Volume targeted ventilation devices:* (e.g. volume control; volume guarantee; pressure regulated volume control, and volume assured pressure support): Eliminating leaks around the endotracheal tube, improving estimation of tidal volume; and minimizing volume loss in ventilatory circuits. • *High-Frequency Ventilators*: Comparative effectiveness research; improved HFV devices during transport
Non-Invasive Ventilation	• *Nasal CPAP and Nasal IMV*: Developing better nasal interfaces for nasal CPAP and non-invasive ventilation; assessing the advantages of synchronization; studies to demonstrate improved long-term outcomes.
Experimental Modalities	*Newer Devices*: ~~Distal tracheal ventilation~~ Distal tracheal ventilation and other methods to reduce dead space ventilation; target minute ventilation: automatic adjustment of ventilator rate to maintain total minute ventilation within target range; automated inspired oxygen control with automatic adjustment of FiO_2 to maintain O_2 saturation within a preset range.

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Pulmonary Function Assessment and other pulmonary devices	• *Bedside assessment of lung volumes:* tools for assessing lung volume and pulmonary mechanics at the bedside, both intermittently and continuously; such measures could help minimize delivered tidal volume, estimate functional residual capacity, and help assess alveolar recruitment, over and under inflation, and ventilation-perfusion in-homogeneity. • *Electrical impedance tomography* –good research to understand what is actually being measured with these devices • *Improved endotracheal tubes* :thinner walls, larger internal lumen; soft enough to avoid airway injury, but firm enough to prevent kinking; with inflatable cuffs to prevent air leaks and help measure pulmonary functions; radio opaque; with fiber optic lights at the tip for accurate position assessment without x-rays; • Nasal laryngeal airways: currently these are too large for babies, but miniaturizing these would be ideal to address aspiration issue
Other Areas	• Developing "Smart alarms" for respiratory monitoring • Developing standard nomenclature for ventilator modalities • Neonatologists/pulmonary experts input prior to device development • Education of personnel about use of the existing and new equipment • Encourage research efforts to assess effects of new and existing devices or strategies on outcome

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From: Webb, Robin E.
To: Webb, Robin E.; sduara@miami.edu; CNavarrete@med.miami.edu; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin
Subject: SUPPORT Call
Date: Tuesday, March 17, 2009 10:35:13 AM

The call to discuss the growth secondary study has been scheduled for:

Wednesday, 4/22

11:00am ET

Dial:

Within the USA

866-675(b) (6)

or

Outside the USA

1-203-310(b) (6)

Then, enter Participant Passcode:

(b) (6)

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From: Susan Hintz
To: BULAS, DOROTHY
Cc: Tom Slovis; <petrie@rti.org>; kristin zaterka; <vanmeurs@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]; <adas@rti.org>; <mcunningham@rti.org>
Subject: Re: central reader CUS form - SUPPORT
Date: Saturday, March 14, 2009 12:45:59 AM

Hi Dorothy

Sounds good. If you and Tom could let us know what you think should be defined up front, and recommendations for the definitions, Kris and/or others can put together a key to go with the form.

Thanks again,

Susan

On Mar 13, 2009, at 1:08 PM, "BULAS, DOROTHY" <DBULAS@cnmc.org> wrote:

> I think the form held up well.. just a few guides on definitions would be helpful
>
> Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Fri 3/13/2009 2:17 PM
To: BULAS, DOROTHY
Cc: Tom Slovis; petrie@rti.org; kristin zaterka; vanmeurs@stanford.edu; higginsr@mail.nih.gov; adas@rti.org; mcunningham@rti.org
Subject: RE: central reader CUS form - SUPPORT

That is a very good idea. We can certainly put together a "key" for definitions as you suggest. But, if you and Tom want to make any changes to the SCORING FORM itself, the changes should really be done within the next week or so. The folks at RTI (data center) will be preparing the imaging including copying forms, filling out the header, and getting things together at the end of March/beginning of April for the central reading.

Thanks - let us know what you think about the scoring forms -

Susan

> We may want to be a bit more specific about how we grede ventriculomegaly - this has been a bit confusing in the past...
>
> mild - minimal third and temp hom??
>
> Mod - third ventricle and temp horn dilated
>
> Severe - cortical thinning?
>
> Measurements may be difficult to obtain
>
> Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thu 3/12/2009 8:37 PM
To: BULAS, DOROTHY
Cc: Tom Slovis; higginsr@mail.nih.gov; kristin zaterka; petrie@rti.org; mcunningham@rti.org; adas@rti.org; vanmeurs@stanford.edu
Subject: central reader CUS form - SUPPORT

Hi all,

Attached is what I have for the most recent cranial US central reader form - probably the last time we all looked at this was in 2005.

Dorothy and Tom - Do you have changes or suggestions to this form before the real fun begins? Please let us know what you think. Now would be the time to make any changes. I am also attaching the MRI central reader form and key for your interest -

Thanks again. It may sound strange, but I am looking forward to the central reading (part #1) in May!

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine

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From: Susan Hintz
To: dorothy bulas
Cc: Tom Slovis; Higgins, Rosemary (NIH/NICHD) [E]; kristin zaterka; petrie@rti.org; mcunningham@rti.org; adas@rti.org; vanmeurs@stanford.edu
Subject: central reader CUS form - SUPPORT
Date: Thursday, March 12, 2009 8:38:00 PM
Attachments: Central ReaderCranial US[MRI04]6-7-05.doc
MRI_Score_keyRev01 23 08 1.doc
MRI Scoring Form MRI03 1-23-08 2.doc

Hi all,

Attached is what I have for the most recent cranial US central reader form - probably the last time we all looked at this was in 2005.

Dorothy and Tom - Do you have changes or suggestions to this form before the real fun begins? Please let us know what you think. Now would be the time to make any changes. I am also attaching the MRI central reader form and key for your interest -

Thanks again. It may sound strange, but I am looking forward to the central reading (part #1) in May!

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

MRI04 Rel 1

June 7, 2005

Support Neuroimaging Secondary

Draft Central Cranial US Reading Form

Center: Network No: Birth No

A. IDENTIFICATION

1. READER: ___ ___ ___ INITIALS

2. DATE READ: __ __/__ __/__ __ __ __ MONTH DAY YEAR

3. READING: ____

4. DATE OF SONOGRAM: ___ ___/___ ___/__ __ __ __

5. QUALITY: GOOD POOR

6. READABLE: YES NO

8. ALL NECESSARY VIEWS AVAILABLE: YES NO

9. NORMAL READING: YES NO

ULTRASOUND RESULTS	Left		Right	
	Yes	No	Yes	No
B. ECHODENSITY SITE				
1. Echodensity present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intraventricular				
1) If Yes,				
< 25 % filled				
25-50 % filled				
> 50% filled				
d. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
5. Thalamus				
6. Posterior Fossa				
e. Other				

	Left		Right	
	Yes	No	Yes	No
C. ECHOLUCENCY SITE				
1. Echolucency present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
d. Parenchymal Cyst				
e. Other				
D. OTHER PARENCHYMAL				
1. Other Parenchymal				
If Yes, mark all that apply				
a. Calcification				
b. Cerebral edema				
c. Cortical atrophy				
d. Extra axial fluid				
e. Infarct				
f. LS Branching				
g. Other				

	Left		Right	
	Yes	No	Yes	No
E. VENTRICLES				
1. Ventricle abnormality				
a. If Yes,				
Mild increase				
Moderate increase				
Severe increase				
Slit Ventricles				
2. Choroid abnormality				
If Yes, mark all that apply				
a. Cyst				
b. Hemorrhage				
c. other				
F. HEMORRHAGE CLASSIFICATION				
1. Hemorrhage				
If Yes,				
a. Papile Classification				
Grade I				
Grade II				
Grade III				
Grade IV				
Indeterminate				
G. STRUCTURAL ABNORMALITIES				
1. Structural abnormality				
If Yes, comments:				

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MRI SCORING KEY (NOTE: All measurements in millimeter)

Revised January 23, 2008 (for SUPPORT)

B. SIGNAL ABNORMALITIES

REGION AND SITE

REGION	CODE	SITE		CODE
CEREBRAL	C	Frontal	cortical	FC
			subcortical	FSC
			periventricular	FPV
		Temporal	cortical	TC
			subcortical	TSC
			periventricular	TPV
		Parietal	**cortical**	PC
			subcortical	PSC
			periventricular	PPV
		occipital	cortical	OC
			subcortical	OSC
			periventricular	OPV
CEREBELLAR	BEL	Vermian		V
		Hemispheric		H
BASAL GANGLIA	BG	Putamen		P
		Caudate		CAU
		Globus Pallidus		GP
THALAMUS	T			
INTERNAL CAPSULE				
Posterior Limb	PLIC			
Anterior Limb	ALIC			
BRAINSTEM	BS	Medulla		
			Ventral	MVen
			Dorsal	MDor
		Pons		
			Ventral	PVen
			Dorsal	PDor
		Midbrain		
			Ventral	MidVen
			Dorsal	MidDor
CORPUS CALLOSUM	CC	Genu		G
		Body		B
		Splenium		SPL
PITUITARY	PIT			
HYPOTHALAMUS	HY			
OPTIC CHIASM	OP			
EXTRA-AXIAL	EX	Subarachnoid		SAR
		Subdural		SDR
		Epidural		EPI
VASCULAR	VAS	Arterial		ART
		Venous		VEN

OTHER OTH

**Note location and specifics at END OF MRI SCORING FORM

SIDE	**CODE**
Right	R
Left	L

T1, T2, FL, GRE, DWI, ADC

INTENSITY	**CODE**
hypointense	H
isointense	I
hyperintense	H

If lesion not seen on sequence code "98"; if sequence not done code "99"

FOCAL/DIFFUSE	**CODE**
if focal code	
punctate	FP
linear	FL
nodular	FN
if diffuse	D
if multifocal code	MF

GM/WM	**CODE**
if gray matter	GM
if white matter	WM

SIZE: Enter MEASURED diameter of lesion, i.e., 3 = 3mm, 4 = 4mm, etc. If multifocal, enter range smallest to largest. If linear, enter measured LENGTH of lesion

TYPE: **GUIDELINES for interpretation**

Cystic/cavitation abnormalities: T1 hypo T2 hyper, FL hypo

Non-Cystic abnormalities: T1 hyper or hypo T2 hyper FL hyper

**Note; T1 hyper in absence of marked T2 hypo is likely gliosis[7]

Hemorrhage or mineralization: GRE hypo +/- T1 hyper and MARKED T2 hypo

Type	**CODE**
Cystic	CYS
Non-Cystic	NCYS
Hemmorhage/Mineral	HMN

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MRI SCORING KEY (NOTE: All measurements in millimeter)

Revised January 23, 2008 (for SUPPORT)

C. MATURATION AND DEVELOPMENT

GRAY MATTER MATURATION [1, 2, 3]

For each hemisphere, mark level of maturation

Stage	Cortical maturation markers
G0	Frontal and occipital cortex completely smooth, insula widely open
G1	Frontal cortex still smooth, but some sluci in occipital cortex
G2	Frontal and occipital cortex with some convolutions, frontal sulci shallow
G3	Frontal and occipital cortex folded and rick in sulci, insula more convoluted and infolded
G4	Secondary gyri present transverse and inferior temporal; anterior and posterior orbit gyri
G5	Teritiary inferior temporal and infereior occipital gyri and sulci present. White matter now isointense with gray matter on T1
NE	Not Evaluable

SUBARACHNOID SPACE Record widest measured at ant./post. IHF, lat. Post. Parietal SAS at centrum semiovale [4]

Normal = <4 mm

Mild-moderate enlargement = 4-6 mm

Marked enlargement = >6 mm

WHITE MATTER MATURATION [1, 5]

For each hemisphere, mark level of maturation noted on both T1 and T2

Stage	Myelination
W0	Immature (<30 week) myelination pattern - i.e. brain stem not myelinated, etc.
W1	brain stem, dorsal aspect of pons
W2	ventral pons, cerebellar medulla
W3	PLIC, lenticular nucleus, thalamus
W4	corona radiata
W5	corticospinal tracts of the precentral and postcentral gyri
NE	Not Evaluable

CORPUS CALLOSUM

Provide SAGITTAL measured width at each of the following

Genu

Body

Splenium

LATERAL VENTRICLE SIZE, ASYMMETRY AND DISPROPORTION [4, 6]

SIZE: Measure ventricular/brain index (V/B index) **ON AXIAL T1 or FLAIR IMAGES**. Enter measured V/B ratio for right and left sides

Frontal horn ABNORMAL = V/B ratio>0.35

Midbody ABNORMAL = V/B ratio>0.35

Trigone ABNORMAL = V/B ratio >0.60

ASYMMETRY:

Mark "yes" in appropriate box if one ventricle is clearly larger than the other

DISPROPORTION:

Record "yes" if clear disproportionate shape of lateral ventricle, including but not limited to "squared"

D. INTRAVENTRICULAR CONTENT

Describe presence or absence of choroid cyst and hemorrhage as indicated.

Describe presence or absence of intraventricular hemorrhage, shunt, and mineralization as indicated

E. OTHER

Record maximum transverse and vertical dimension of fourth ventricle and maximum transverse dimension of third ventricle in mm.

BIBLIOGRAPHY

1. Huppi P, et. al. Peds Res 1996;39:895-901
2. Inder T, et. al. J Pediatr 2003;143:171-179
3. Childs A-M, et. al. AJNR 2001;22:1577-1582
4. Valkama AM, et. al. Acta Paediatr 2000;89:348-355
5. Counsell S, et. al. AJNR 2002;23:872-881
6. Poland RL, Slovis TL, Shankaran S. Pediatr Radiol 1985;15:12-14
7. Miller SP,et. al. AJNR 2003; 24:1661-1669

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NICU Network

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)
CENTRAL MRI READING FORM

MRI03
January 23, 2008

Center: __ __ Site __ Network No: __ __ __ __

GENERAL INFORMATION

A. IDENTIFICATION

1. READER: __ __ __ Initials
2. DATE READ: __ __/__ __/__ __ __ __ MONTH DAY YEAR
3. DATE OF MRI: __ __/__ __/__ __ __ __ MONTH DAY YEAR
4. PCA IN WEEKS AND DAYS AT MRI: __ __ . __
5. QUALITY: GOOD POOR
6. READABLE: YES NO
7. ALL NECESSARY SEQUENCES, If No, what is missing? _____ YES NO
8. NORMAL READING: If No, completed the remainder of the form YES NO

MRI READING

B. SIGNAL ABNORMALITIES:

1. Are signal abnormalities present? Yes No
   If No, continue to "Maturation and Development" Section.
   If Yes, describe each lesion below:

Lesion Number:	Region	Site	Side	T1	T2	FL	GRE	Focal/Dif	GM/ WM	Size	TYPE
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

If more than 10 lesions, complete additional signal abnormality sheet.

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C. MATURATION AND DEVELOPMENT:

1. GRAY MATTER

a. Cortical maturation markers (check only one appropriate box per each hemisphere)

	Left	Right
1. G 0		
2. G 1		
3. G 2		
4. G 3		
5. G 4		
6. G 5		
7. Not Evaluable		

b. Subarachnoid space enlargement (check only one appropriate per for each hemisphere)

	Left	Right
1. Normal		
2. mild-mod		
3. Marked		

2. WHITE MATTER

a. Markers of myelination (Check only one appropriate box per hemisphere for T1 and T2))

	Left		Right	
	T1	T2	T1	T2
1. W 0				
2. W 1				
3. W 2				
4. W 3				
5. W 4				
6. W 5				
7. Not Evaluable				

b. Corpus Callosum Measured Width (Sagittal view)

1. genu	__ __ __ mm
2. body	__ __ __ mm
3. splenium	__ __ __ mm

c. Lateral Ventricle Size

V/B INDEX Abnormal?	Left		Right	
	Yes	No	Yes	No
1. Frontal horn				
2. Midbody				
3. Trigone				

d. Lateral Ventricle asymmetry and disproportion Yes No

If Yes, complete below:

	Yes	No
1. Left greater than right		
2. Right greater than left		
3. Right disproportion		
4. Left disproportion		

D. INTRAVENTRICULAR CONTENT

	Left		Right	
	Yes	No	Yes	No
1. Choroid cyst				
2. Choroid hemorrhage				
3. LATERAL VENTRICLES				
A. Hemorrhage?				
1. Grade I				
2. Grade II				
3. Grade III				
4. Grade IV				
B. Shunt present?				
C. Mineralization present?				

E. OTHER

		Measured size
1. THIRD VENTRICLE	Transverse	
2. FOURTH VENTRICLE	Transverse	
	Vertical	

	Left		Right	
3. STRUCTURAL ABNORMALITIES	Yes	No	Yes	No

COMMENTS:

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From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, March 11, 2009 4:42:40 PM

We are on it!

Thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970(b) (6)
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

03/11/2009 04:09 PM

To <Kimberley.fisher@Duke.edu>
cc
Subject Re: SUPPORT

This is becoming time critical as we have completed recruitment and plan to do the analysis mid-late summer.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist
NICHD

From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Mar 11 15:58:34 2009
Subject: Re: SUPPORT

Rose
I have gotten in contact with the person that can provide this information for me and I will stay on it until I have these missing pieces put into the database. I am so sorry that it has taken me so long to get on this but it will be done.

Thanks
Kim

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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

02/18/2009 03:00 PM

To <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Kimberley A Fisher" <kimberley.fisher@duke.edu>
cc "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
Thanks for all the effort!!!!
Rose

CENTER NETWORK ROP_message

19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health

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From: Cunningham, Meg
To: Susan Hintz; BULAS, DOROTHY
Cc: Tom Slovis; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Higgins, Rosemary (NIH/NICHD) [E]; vanmeurs@stanford.edu; Das, Abhik
Subject: SUPPORT neuroimaging secondary central reading dates
Date: Wednesday, March 11, 2009 2:44:29 PM

Hi All,

The first central reading will take place on May 10-11, 2009 in Washington DC. The second meeting will be scheduled following the first meeting.

Please let me know if you have any questions.

Meg

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, March 04, 2009 1:35 PM
To: BULAS, DOROTHY
Cc: Tom Slovis; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Cunningham, Meg; higginsr@mail.nih.gov; vanmeurs@stanford.edu; Das, Abhik
Subject: RE: SUPPORT neuroimaging secondary - cranial US

Hi all

I got a couple days of coverage for May 10-11 dates - so I could do that for sure -

Susan

the May dates are best for me

Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wed 3/4/2009 11:37 AM
To: Cunningham, Meg
Cc: higginsr@mail.nih.gov; BULAS, DOROTHY; Tom Slovis; vanmeurs@stanford.edu; petrie@rti.org; kristin zaterka; adas@rti.org
Subject: RE: SUPPORT neuroimaging secondary - cranial US

If I can get coverage for my clinical duties for 2 days, I could do May 10-11. I can also do June 28 and 29.

I assume this is for the FIRST of the 2 central readings. I am skeptical that we will have all (or nearly all) the CUS in to RTI even by June 28, but I know Rose and RTI can work miracles - so maybe I should be optimistic. I would think the 2nd and final central reading might be better scheduled for the summer? Like early August?

Susan

So here are the three possibilities for meetings. Which of these will work best for you all?

Sunday, May 10 - Monday May 11 in Washington, DC

Sunday, May 17 - Monday, May 18 in Washington, DC or Detroit

Sunday, June 28 - Monday, June 29 in Detroit

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Tuesday, March 03, 2009 6:18 PM
To: Slovis, Thomas; Cunningham, Meg; srhintz@stanford.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

Can we do in Washington DC for this review and then detroit?

April 13, 20 not good

April 27 might work.

May 4 not good

May 11 , May 18 could work

June 29 could work - we could work Sunday and monday... fridays not good for me mondays the best.

Dorothy Bulas MD

From: Slovis, Thomas [mailto:tslovis@med.wayne.edu]
Sent: Tue 3/3/2009 4:18 PM
To: Cunningham, Meg; srhintz@stanford.edu; BULAS, DOROTHY
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

the SPR meeting is the week of April 21. Let 's decide if we do a weekend plus a Monday or Friday to minimize time away from work. ESPR is first week of June. Tom

---

From: Cunningham, Meg [mcunningham@rti.org]

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Sent: Tuesday, March 03, 2009 12:19 PM
To: Slovis, Thomas; srhintz@stanford.edu; DBULAS@cnmc.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: FW: SUPPORT neuroimaging secondary - cranial US

Hello All-

Please provide your availability below so we can finalize dates for these meetings. The first meeting will be held in DC and the second will be held in either NC or Detroit. For the weeks listed below, please indicate which days you would not be available to meet.

Week of:

April 13th -

April 20th -

April 27th -

May 4th -

May 11th -

May 18th -

May 25th -

June 1st -

June 8th -

June 15th -

June 22nd -

June 29th -

Thanks,
Meg

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Monday, March 02, 2009 4:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz
Cc: tslovis@med.wayne.edu; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Das, Abhik; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

(b) (6) a visit there could work as well! I could drive - Tom how about Durham over Detroit for the second visit - you love to travel dont you?
Dorothy Bulas MD

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 3/2/2009 4:09 PM
To: BULAS, DOROTHY; Susan Hintz
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US
The NC location is at RTI - Research Triangle Park (Raleigh-Durham airport is very close).

Thanks
Rose

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Monday, March 02, 2009 4:05 PM
To: Susan Hintz
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

I think 2 days each time might work - it depends on how the images are transfered... are they still all on disc?

It would be great to start with a 2 day meeting and see how fast it goes - hopefully Tom would be up to coming to DC. the schedule is tight this spring for me.

I could get room for us at CNMC.

Let me know TOM if a trip to DC would work for you. Where in NC is your data base?

Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Mon 3/2/2009 3:42 PM
To: BULAS, DOROTHY
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; higginsr@mail.nih.gov; vanmeurs@stanford.edu; srhintz@stanford.edu
Subject: SUPPORT neuroimaging secondary - cranial US

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Hi Dorothy and Tom,

It has been about 2 years since we last spoke about the "way far away" end of the SUPPORT trial - and the beginning of the central reading of the CUS for the Neuroimaging and Neurodevelopmental Secondary of that trial. Well, the time has come! The last patient was enrolled last week, so we would like to start planning and thinking about the process of the central reading.

As I explained when we first communicated about this trial, we will have 2 CUS from each of the ~500-550 patients that are enrolled in the neuroimaging secondary and survive to 36 weeks (one at <14 days and one at ~36 weeks PMA). We will also have an MRI at ~36 weeks for each of these patients - Pat Barnes will be central reader for those. We now are very excited to have not only 18-22 month neurodevelopmental follow-up funded, but ALSO 6-7 year follow-up. This will really be a great opportunity for us to evaluate the predictive capabilities of early and late CUS, compare with MRI, the contribution of neuroimaging to outcomes prediction in general for extremely preterm infants, and importantly to assess differences in neuroimaging abnormalities with respect to randomized interventions of oxygen saturation targets and ventilation strategies. This will be the largest preterm cohort in the world with complete, centrally-read neuroimaging and neurodevelopmental follow-up, and the only one to date with exclusively extremely preterm infants (<28 weeks). We will also be the first

When we communicated previously, it sounded like you both were in favor of at least an attempt at an "omnibus" central reading rather than getting them sent to you individually in drips and drabs. I agree in principal that this is the best approach so we can have support and helpers from the data center to help fill in the forms while you read, making things move faster. However, with ~1100 CUS, I wonder if this could really be accomplished in one single central reading event. So, my questions to you are:

1) How long will this take?: Since you have both been involved in so many trials as central readers, you will of course have a better estimate than I for how long/ how many hours and days it will take to read this many CUS. Is it reasonable to plan for 2 x central reading "events" - perhaps 2-3 days each? Contrasting with the Premie iNO central reading - a) there were fewer cranial US for PiNO than we will have for SUPPORT, b) all the PiNO CUS were not able to be read during the one central reader event, thus you both had to finish up on your own (which was probably not so easy and made things go more slowly), but c) the severity of illness for the PiNO patients was MUCH greater than for the SUPPORT patients, and I would expect that the CUS will not be as complex to read as those.

2) Location: We could do the central reading in D.C. (as we did with PiNO, as long as Dorothy can get us the space), or in North Carolina where the data center is located, or in Detroit (as long as Tom can get us the space). If we have two central reading events, we could do one close to Dorothy and one close to Tom. In any case, the data center has committed to providing "helpers" no matter where the readings occur!

3) Deadlines: We do not have all the CUS at the data center yet - some of the patients have not even reached the 36 week mark - but we have many. Also, we would love to have the readings completed by early fall 2009 (September) in order to potentially make the late breaker deadline for PAS. So, we would like to plan for a first central reading event as soon as practicable for you both. Carolyn Petrie Huitema (who helped to organize the PiNO central reading) and Kris Zaterka from RTI have been cc'd on this email and they will be helping to schedule all of this with you both.

4) Contract issues: I am not in the loop about the contracting and remuneration side of this - but Dr. Abhik Das from RTI will be the initial point person for those discussions with you both. He is also cc'd on this email.

OK - that is it for now. We are truly excited about this trial, and about the information we can provide for care providers and families. I am also very excited to continue communications with you about ideas for other analyses for these neuroimaging data we can work on together - we have a very, very rich database for these patients, and this will be an exciting and unique opportunity to learn more!

Thanks,

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
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From:	Webb, Robin E.
To:	Webb, Robin E.; alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu; Poole, W. Kenneth; mcw3@cwru.edu
Cc:	sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin; Carolyn.Grier@UHhospitals.org
Subject:	SUPPORT subcommittee Call
Date:	Tuesday, March 10, 2009 3:41:48 PM

The call to discuss plans for data analysis and mock tables has been scheduled for:

Monday, 3/30
11:00am ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6) #

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From: Cunningham, Meg
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Huitema, Carolyn Petrie; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT neuroimaging secondary - cranial US
Date: Thursday, March 05, 2009 11:52:45 AM

Thanks! I think we should wait until after the first meeting to schedule the second. By then we will know if we should schedule a 2 or 3 day meeting.

From: Zaterka-Baxter, Kristin
Sent: Thursday, March 05, 2009 11:02 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Cunningham, Meg
Cc: Huitema, Carolyn Petrie; Das, Abhik; Gantz, Marie
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Subject: RE: SUPPORT neuroimaging secondary - cranial US

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June 22nd -

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Sent: Monday, March 02, 2009 4:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz

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Cc: tslovis@med.wayne.edu; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Das, Abhik; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

(b) (6) so a visit there could work as well! I could drive - Tom how about Durham over Detroit for the second visit - you love to travel dont you?
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Subject: RE: SUPPORT neuroimaging secondary - cranial US
The NC location is at RTI - Research Triangle Park (Raleigh-Durham airport is very close).

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I could get room for us at CNMC.

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3) Deadlines: We do not have all the CUS at the data center yet - some of the patients have not even reached the 36 week mark - but we have many. Also, we would love to have the readings completed by early fall 2009 (September) in order to potentially make the late breaker deadline for PAS. So, we would like to plan for a first central reading event as soon as practicable for you both. Carolyn Petrie Huitema (who helped to organize the PiNO central reading) and Kris Zaterka from RTI have been cc'd on this email and they will be helping to schedule all of this with you both.

4) Contract issues: I am not in the loop about the contracting and remuneration side of this - but Dr. Abhik Das from RTI will be the initial point person for those discussions with you both. He is also cc'd on this email.

OK - that is it for now. We are truly excited about this trial, and about the information we can provide for care providers and families. I am also very excited to continue communications with you about ideas for other analyses for these neuroimaging data we can work on together - we have a very, very rich database for these patients, and this will be an exciting and unique opportunity to learn more!

Thanks,

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Susan

--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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From: Huitema, Carolyn Petrie
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT neuroimaging secondary - cranial US
Date: Thursday, March 05, 2009 11:13:04 AM

I can be available after July 21st.

From: Zaterka-Baxter, Kristin
Sent: Thursday, March 05, 2009 11:02 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Cunningham, Meg
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Thanks,

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Susan

--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
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From: Cunningham, Meg
To: Huitema, Carolyn Petrie; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT neuroimaging secondary - cranial US
Date: Thursday, March 05, 2009 9:41:28 AM

I think way back in this email string we decided to start with a two day meeting, and then adjust the second meeting if we thought more time was needed.

I will check with Dr. Hintz about her plans after PAS.

From: Huitema, Carolyn Petrie
Sent: Thursday, March 05, 2009 9:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

From Dr. Slovis's email I get the sense he is looking for a Sat/Sun plus either a Mon or Fri.
And if Dr. Hintz stays on the east coast after PAS, the group may wish to start on Saturday, May 9, scheduling their departure flights around 3pm on Monday.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 05, 2009 9:31 AM
To: Cunningham, Meg; Zaterka-Baxter, Kristin
Cc: Huitema, Carolyn Petrie; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

I am ok with this time frame.

We need to start generating lists of missing CUS and MRI studies and I will remind the sites

Second reading may need to be a little later in order to insure having the bulk of the studies.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Thursday, March 05, 2009 8:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Huitema, Carolyn Petrie; Das, Abhik
Subject: FW: SUPPORT neuroimaging secondary - cranial US

So it seems like we could go with May 10-11 in DC. Should I confirm this with the group?

A couple of questions:

She would we wait on setting up the 2nd weekend?
Kris is talking to Marie this morning to see when the last kid will reach 42 weeks to see if we will have all CUS returned to RTI by June.
If we do the second reading at the end of June, this will follow the NRN SC meeting, which means Kris and Susan will be in DC, so this may be a good option and a good reason to hold the second training in DC.

Thoughts?

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, March 04, 2009 1:35 PM
To: BULAS, DOROTHY
Cc: Tom Slovis; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Cunningham, Meg; higginsr@mail.nih.gov; vanmeurs@stanford.edu; Das, Abhik
Subject: RE: SUPPORT neuroimaging secondary - cranial US

Hi all

I got a couple days of coverage for May 10-11 dates - so I could do that for sure -

Susan

the May dates are best for me

Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wed 3/4/2009 11:37 AM
To: Cunningham, Meg
Cc: higginsr@mail.nih.gov; BULAS, DOROTHY; Tom Slovis; vanmeurs@stanford.edu; petrie@rti.org; kristin zaterka; adas@rti.org
Subject: RE: SUPPORT neuroimaging secondary - cranial US

If I can get coverage for my clinical duties for 2 days, I could do May 10-11. I can also do June 28 and 29.

I assume this is for the FIRST of the 2 central readings. I am skeptical that we will have all (or nearly all) the CUS in to RTI even by June 28, but I know Rose and RTI can work miracles - so maybe I should be optimistic. I would think the 2nd and final central reading might be better scheduled for the summer? Like early August?

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Susan

So here are the three possibilities for meetings. Which of these will work best for you all?

Sunday, May 10 - Monday May 11 in Washington, DC

Sunday, May 17 - Monday, May 18 in Washington, DC or Detroit

Sunday, June 28 - Monday, June 29 in Detroit

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Tuesday, March 03, 2009 6:18 PM
To: Slovis, Thomas; Cunningham, Meg; srhintz@stanford.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

Can we do in Washington DC for this review and then detroit?

April 13, 20 not good

April 27 might work.

May 4 not good

May 11 , May 18 could work

June 29 could work - we could work Sunday and monday... fridays not good for me mondays the best.

Dorothy Bulas MD

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Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: RE: SUPPORT neuroimaging secondary - cranial US

the SPR meeting is the week of April 21. Let 's decide if we do a weekend plus a Monday or Friday to minimize time away from work. ESPR is first week of June. Tom

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Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: FW: SUPPORT neuroimaging secondary - cranial US

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June 1st -

June 8th -

June 15th -

June 22nd -

June 29th -

Thanks,
Meg

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Monday, March 02, 2009 4:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz
Cc: tslovis@med.wayne.edu; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Das, Abhik; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

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(b) (6) a visit there could work as well! I could drive - Tom how about Durham over Detroit for the second visit - you love to travel dont you?
Dorothy Bulas MD

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 3/2/2009 4:09 PM
To: BULAS, DOROTHY; Susan Hintz
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US
The NC location is at RTI - Research Triangle Park (Raleigh-Durham airport is very close).

Thanks
Rose

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I could get room for us at CNMC.

Let me know TOM if a trip to DC would work for you. Where in NC is your data base?

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From: Susan Hintz [mailto:srhintz@stanford.edu]
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To: BULAS, DOROTHY
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; higginsr@mail.nih.gov; vanmeurs@stanford.edu; srhintz@stanford.edu
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Susan

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Susan R. Hintz, M.D., M.S. Epi
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Palo Alto, CA 94304
ph: 650-723-5711
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From: Zaterka-Baxter, Kristin
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Huitema, Carolyn Petrie
Subject: FW: SUPPORT neuroimaging secondary - cranial US
Date: Wednesday, March 04, 2009 9:38:55 AM

Hi all,

The concern I have about reading these HUS in Detroit is the logistics of moving the US around. It makes sense to me to read them all in DC because we can house all scans at RTIs DC or Rockville office (I can drive them up for the first reading and then they can read as many as possible and we can bring the rest back to RTI to be read another day). If we go to Detroit not only do we have to bring the US up there, we might have to bring some back un-read if there is not enough time. I just think it leaves a lot of room for images to get damaged or lost.

Currently per the data there are 484 complete cases (MRI plus both HUS). Right now I have 163 HUS on films and over 250 HUS on CD (the majority of the CDs are per case so they have both early and late on one CD) in my office. I will send out a reminder to the sites to send the images in asap.

Thanks,
Kris

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Sent: Tuesday, March 03, 2009 6:18 PM
To: Slovis, Thomas; Cunningham, Meg; srhintz@stanford.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
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fax: 650-725-8351

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From:	Zaterka-Baxter, Kristin
To:	ahensman@wihri.org; Archer, Stephanie (NIH/NICHD) [E]; Bethany Ball; BMackinnon@tuftsmedicalcenter.org; Conra Lacy; Cunningham, Meg; ellen_hale@oz.ped.emory.edu; Faithe Hammer; Georgia.E.McDavid@uth.tmc.edu; grisbyca@email.uc.edu; Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Johnson, Karen; karen.osborne@hsc.utah.edu; ldw@iupui.edu; mcollins@peds.uab.edu; melissa.leps@utsouthwestern.edu; monica.konstantino@yale.edu; nancy newman; Nancy.Miller@UTSouthwestern.edu; Newman, Jamie; rbara@med.wayne.edu; Michelle Tidwell; Shirley Cosby; Poundstone, Margaret ; Kimberley A Fisher; Everett-Thomas, Ruth; Rich, Wade; npeters@wfubmc.edu; Reubens, Linda
Cc:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	Support Trial Oximeter Returns
Date:	Tuesday, March 03, 2009 5:33:18 PM
Attachments:	SUPPORTCoordinators_Updated20090303.DOC SUPPORT Oximeter by Center Home 20080131.pdf

Dear all,

Now that the Support trial has completed enrollment and as your remaining infants complete the study per protocol; please return the study Masimo oximeters to their original institutions (Oximeter owner in the attached pdf file). Please also find attached an updated address list (Support Coordinator file attached) to include addresses for Miami, Wake Forest, Rochester and UCSD. Please clean all equipment and include sensors and probes prior to sending them home. For those oximeters currently being repaired at Masimo, please send the original institution an email listing the serial number being repaired and send that oximeter on once received back from Masimo.

Thank you all very much,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
Brown University	Angelita Hensman, R.N.C. Department of Pediatrics Women & Infant's Hospital 101 Dudley Street, Room 1136 Providence, RI 02905 ahensman@wihri.org (401) 274-1100 ext. 1730
Case Western Reserve University	Nancy Newman, R.N. University Hospitals Case Medical Center Rainbow Babies & Children's Hospital 11100 Euclid Ave., Room 3100 Cleveland, OH 44106-6010 nxs5@cwru.edu (216) 368-3084
Duke University	Kim Fisher, PhD, FNP, IBCLC Division of Neonatology Duke University Medical Center 204 Bell Building, Rm 141 Durham, NC 27710 foy00004@mc.duke.edu (919) 668-3360
Emory University	Ellen Hale, R.N.C., B.S. 3267 Sutcliffe Ridge Marietta, GA 30064 ellen_hale@oz.ped.emory.edu 678-232-7102.
Indiana University	Leslie Dawn Wilson, RN, BSN Research Manager Neonatal Network Coordinator Riley Hospital RR 208 699 West Dr Indianapolis, IN 46202 ldw@iupui.edu (317) 274-8255
Rochester University	Linda Reubens, R.N 601 Elmwood Ave., Box 651 Rochester, NY 14642 linda_reubens@urmc.rochester.edu (585) 275-0218

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
Stanford University	M. Bethany Ball Stanford University Division of Neonatology 750 Welch Road, Suite 315 Palo Alto, CA 94304 mbball@stanford.edu (650) 725-8342
Tufts University	Brenda MacKinnon, RNC, Floating Hospital for Children at Tufts Medical Center 800 Washington Street Newborn Medicine, Floating 2, Box 44 Boston, MA 02111 bmackinnon@tuftsmedicalcenter.org 617-636-1218; Beeper #(b)
University of Alabama	Monica Collins, RN, MaEd Division of Neonatology University of Alabama at Birmingham 525 New Hillman Building 619 South 19th St Birmingham, AL 35233 mcollins@peds.uab.edu (205) 934-5771
University of California, San Diego	Wade Rich University of California--San Diego 402 Dickerson St MPF 1-140 San Diego, CA 92103 wrich@ucsd.edu (619) 543-3759
University of Cincinnati	Cathy Grisby, R.N. Cincinnati Children's Hospital (S Building) 9th Floor/Room S9.303 240 Albert Sabin Way Cincinnati 45229-2842 grisbyca@email.uc.edu (513) 803-0950

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
University of Iowa	Karen J. Johnson, R.N. Department of Pediatrics University of Iowa 200 Hawkins Drive, 8900 JPP Iowa City, IA 52242 karen-johnson@uiowa.edu 319-356-2924
University of Miami	Ruth Everett-Thomas, PhD Central Building, Suite 740 Jackson Memorial Hospital 1611 NW 12 Avenue Miami, FL 33136 REverett@med.miami.edu (305) 585-6408
University of New Mexico	Conra Lacy, R.N. Department of Pediatrics 915 Camino de Salud NE Albuquerque NM 87131 cbackstrom@salud.unm.edu 505-272-0367
University of Texas – Dallas	Nancy Miller, R.N. and Melissa H. Leps, R.N. (Co-Coordinator) Department of Pediatrics University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., E3 404 Dallas, TX 75235-9063 Nancy.Miller@utsouthwestern.edu melissa.leps@utsouthwestern.edu (214) 648-3780
University of Texas – Houston	Georgia McDavid, R.N. Department of Pediatrics University of Texas-Houston 6431 Fannin, Suite 3.252, Medical Sciences Building Houston, TX 77030-1501 Georgia.E.McDavid@uth.tmc.edu (713) 500-5734

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Research Coordinators at the NICHD Neonatal Network Sites for The SUPPORT Study	
Name of Center	**Network Coordinator Contact Information**
University of Utah	Karen Osborne, RN BSN Neonatal Research Network University of Utah The Williams Building Dept of Pediatrics, Division of Neonatology Salt Lake City, UT 84158 karen.osborne@hsc.utah.edu (801) 213-3298
Wayne State University	Becky Bara, RN, BSN or Division of Neonatal & Perinatal Medicine Children's Hospital of Michigan Dept. of Neonatology, #4C19 3901 Beaubien Blvd. Detroit, MI 48201 rbara@med.wayne.edu (313) 745-1436
Wake Forest University	Nancy Peters, R.N. Wake Forest University Health Sciences, Department of Pediatrics/Neonatology, Medical School Blvd. Winston-Salem, NC 27157 npeters@wfubmc.edu (336) 716-6911
Yale University	Monica Konstantino, R.N. Yale-New Haven Children's Hospital 20 York St. WP493 New Haven, CT 06504 monica.konstantino@yale.edu (203)688-7987

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Serial Numbers *Updated 1/31/08*	Color Codes	Oximeter Home (During study)	Oximeter Owner (From 1 mo. to study)
310716	BLUE	CENTER 3	CENTER 3
310725	ORANGE	CENTER 3	CENTER 3
310878	BLUE	CENTER 3	CENTER 3
310879	ORANGE	CENTER 3	CENTER 3
310881	BLUE	CENTER 3	CENTER 3
310884	BLUE	CENTER 3	CENTER 3
310886	ORANGE	CENTER 3	CENTER 3
310949	ORANGE	CENTER 3	CENTER 3
323319	BLUE	CENTER 3	CENTER 3
323320	ORANGE	CENTER 3	CENTER 3
323321	BLUE	CENTER 3	CENTER 3
323325	BLUE	CENTER 3	CENTER 3
323326	BLUE	CENTER 3	CENTER 3
323328	BLUE	CENTER 3	CENTER 3
310906	ORANGE	CENTER 4	CENTER 4
311179	BLUE	CENTER 4	CENTER 4
311194	ORANGE	CENTER 4	CENTER 4
311217	ORANGE	CENTER 4	CENTER 4
311320	ORANGE	CENTER 4	CENTER 4
311384	BLUE	CENTER 4	CENTER 4
311438	BLUE	CENTER 4	CENTER 4
311440	BLUE	CENTER 4	CENTER 4
313007	BLUE	CENTER 5	CENTER 5
313415	ORANGE	CENTER 5	CENTER 5
313468	ORANGE	CENTER 5	CENTER 5
313469	ORANGE	CENTER 5	CENTER 5
313470	BLUE	CENTER 5	CENTER 5
313471	BLUE	CENTER 5	CENTER 5
313542	ORANGE	CENTER 5	CENTER 5
313554	ORANGE	CENTER 5	CENTER 5
313560	ORANGE	CENTER 5	CENTER 5
313580	BLUE	CENTER 5	CENTER 5
313586	BLUE	CENTER 5	CENTER 5
313713	BLUE	CENTER 5	CENTER 5
313042	BLUE	CENTER 9	CENTER 9
313055	BLUE	CENTER 9	CENTER 9
313058	ORANGE	CENTER 9	CENTER 9
313072	BLUE	CENTER 9	CENTER 9
313082	BLUE	CENTER 9	CENTER 9
313085	ORANGE	CENTER 9	CENTER 9
313086	ORANGE	CENTER 9	CENTER 9
313089	ORANGE	CENTER 9	CENTER 9
313092	BLUE	CENTER 9	CENTER 9
313186	ORANGE	CENTER 9	CENTER 9
323078	ORANGE	CENTER 9	CENTER 9
323085	BLUE	CENTER 9	CENTER 9
323086	ORANGE	CENTER 9	CENTER 9
323087	BLUE	CENTER 9	CENTER 9
310719	ORANGE	CENTER 11	CENTER 11
310720	BLUE	CENTER 11	CENTER 11
310730	ORANGE	CENTER 11	CENTER 11
310744	BLUE	CENTER 11	CENTER 11
310749	BLUE	CENTER 11	CENTER 11
310751	BLUE	CENTER 11	CENTER 11
310762	ORANGE	CENTER 11	CENTER 11
310771	ORANGE	CENTER 11	CENTER 11
310778	BLUE	CENTER 11	CENTER 11
310805	BLUE	CENTER 11	CENTER 11
310882	ORANGE	CENTER 11	CENTER 11

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310885	BLUE	CENTER 11	CENTER 11
310931	BLUE	CENTER 11	CENTER 11
310947	ORANGE	CENTER 11	CENTER 11
310948	ORANGE	CENTER 11	CENTER 11
311019	ORANGE	CENTER 11	CENTER 11
302324	BLUE	CENTER 12	CENTER 12
311695	BLUE	CENTER 12	CENTER 12
312058	BLUE	CENTER 12	CENTER 12
312163	ORANGE	CENTER 12	CENTER 12
312169	ORANGE	CENTER 12	CENTER 12
312196	ORANGE	CENTER 12	CENTER 12
312198	ORANGE	CENTER 12	CENTER 12
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312203	BLUE	CENTER 12	CENTER 12
312228	ORANGE	CENTER 12	CENTER 12
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312250	ORANGE	CENTER 12	CENTER 12
312251	ORANGE	CENTER 12	CENTER 12
312333	BLUE	CENTER 12	CENTER 12
312334	ORANGE	CENTER 12	CENTER 12
312341	BLUE	CENTER 12	CENTER 12
310828	ORANGE	CENTER 13	CENTER 13
310896	BLUE	CENTER 13	CENTER 13
310936	BLUE	CENTER 13	CENTER 13
310969	ORANGE	CENTER 13	CENTER 13
311002	ORANGE	CENTER 13	CENTER 13
311128	ORANGE	CENTER 13	CENTER 13
311203	ORANGE	CENTER 13	CENTER 13
311319	BLUE	CENTER 13	CENTER 13
311344	ORANGE	CENTER 13	CENTER 13
311388	BLUE	CENTER 13	CENTER 13
311411	BLUE	CENTER 13	CENTER 13
311467	BLUE	CENTER 13	CENTER 13
310241	BLUE	CENTER 14	CENTER 14
310718	ORANGE	CENTER 14	CENTER 14
310721	BLUE	CENTER 14	CENTER 14
310726	BLUE	CENTER 14	CENTER 14
310743	ORANGE	CENTER 14	CENTER 14
310757	ORANGE	CENTER 14	CENTER 14
310775	BLUE	CENTER 14	CENTER 14
310916	ORANGE	CENTER 14	CENTER 14
310930	ORANGE	CENTER 14	CENTER 14
310932	BLUE	CENTER 14	CENTER 14
310933	ORANGE	CENTER 14	CENTER 14
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313019	BLUE	CENTER 14	CENTER 14
313361	ORANGE	CENTER 14	CENTER 14
313408	ORANGE	CENTER 14	CENTER 14
313540	BLUE	CENTER 14	CENTER 14
313558	BLUE	CENTER 14	CENTER 14
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338427	BLUE	CENTER 14	CENTER 14
338428	ORANGE	CENTER 14	CENTER 14
338429	BLUE	CENTER 14	CENTER 14
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312051	ORANGE	CENTER 15	CENTER 15
312232	BLUE	CENTER 15	CENTER 15

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312244	ORANGE	CENTER 15	CENTER 15
312247	BLUE	CENTER 15	CENTER 15
311530	BLUE	CENTER 16	CENTER 16
311557	ORANGE	CENTER 16	CENTER 16
311576	ORANGE	CENTER 16	CENTER 16
312095	BLUE	CENTER 16	CENTER 16
312116	ORANGE	CENTER 16	CENTER 16
312119	BLUE	CENTER 16	CENTER 16
312125	BLUE	CENTER 16	CENTER 16
312131	BLUE	CENTER 16	CENTER 16
312133	ORANGE	CENTER 16	CENTER 16
312172	ORANGE	CENTER 16	CENTER 16
312192	ORANGE	CENTER 16	CENTER 16
312214	ORANGE	CENTER 16	CENTER 16
312225	BLUE	CENTER 16	CENTER 16
312229	ORANGE	CENTER 16	CENTER 16
312233	BLUE	CENTER 16	CENTER 16
312242	ORANGE	CENTER 16	CENTER 16
312260	ORANGE	CENTER 16	CENTER 16
312268	BLUE	CENTER 16	CENTER 16
312272	BLUE	CENTER 16	CENTER 16
312283	BLUE	CENTER 16	CENTER 16
317219	BLUE	CENTER 16	CENTER 8
317227	ORANGE	CENTER 16	CENTER 8
317363	BLUE	CENTER 16	CENTER 8
317384	ORANGE	CENTER 16	CENTER 8
317420	BLUE	CENTER 16	CENTER 8
317431	BLUE	CENTER 16	CENTER 8
317438	ORANGE	CENTER 16	CENTER 8
317560	ORANGE	CENTER 16	CENTER 8
310562	BLUE	CENTER 18	CENTER 18
310727	ORANGE	CENTER 18	CENTER 18
310818	BLUE	CENTER 18	CENTER 18
310821	BLUE	CENTER 18	CENTER 18
310836	ORANGE	CENTER 18	CENTER 18
310839	ORANGE	CENTER 18	CENTER 18
310862	BLUE	CENTER 18	CENTER 18
310869	ORANGE	CENTER 18	CENTER 18
310873	ORANGE	CENTER 18	CENTER 18
310877	BLUE	CENTER 18	CENTER 18
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310893	BLUE	CENTER 18	CENTER 18
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311004	ORANGE	CENTER 19	CENTER 20
315452	BLUE	CENTER 19	CENTER 19
316381	BLUE	CENTER 19	CENTER 19
316382	ORANGE	CENTER 19	CENTER 19
316506	BLUE	CENTER 19	CENTER 19
316611	ORANGE	CENTER 19	CENTER 19
316774	BLUE	CENTER 19	CENTER 19
316779	BLUE	CENTER 19	CENTER 19
316783	ORANGE	CENTER 19	CENTER 19
316790	ORANGE	CENTER 19	CENTER 19
310937	BLUE	CENTER 22	CENTER 22
310989	BLUE	CENTER 22	CENTER 22

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310846	ORANGE	CENTER 22	CENTER 20
310912	BLUE	CENTER 22	CENTER 20
310914	BLUE	CENTER 22	CENTER 20
310939	BLUE	CENTER 22	CENTER 20
310944	BLUE	CENTER 22	CENTER 20
310945	BLUE	CENTER 22	CENTER 20
310958	ORANGE	CENTER 22	CENTER 20
310962	BLUE	CENTER 22	CENTER 20
318351	BLUE	CENTER 22	CENTER 22
318859	BLUE	CENTER 22	CENTER 22
323322	ORANGE	CENTER 22	CENTER 8
323323	ORANGE	CENTER 22	CENTER 8
323324	ORANGE	CENTER 22	CENTER 8
323327	ORANGE	CENTER 22	CENTER 8
310834	ORANGE	CENTER 23	CENTER 20
310838	ORANGE	CENTER 23	CENTER 20
310983	ORANGE	CENTER 23	CENTER 20
311139	ORANGE	CENTER 23	CENTER 20
317217	ORANGE	CENTER 23	CENTER 8
317393	BLUE	CENTER 23	CENTER 8
317398	ORANGE	CENTER 23	CENTER 8
317399	ORANGE	CENTER 23	CENTER 8
317408	BLUE	CENTER 23	CENTER 8
310717	BLUE	CENTER 24	CENTER 21
310723	ORANGE	CENTER 24	CENTER 21
310724	ORANGE	CENTER 24	CENTER 21
310729	ORANGE	CENTER 24	CENTER 21
310734	BLUE	CENTER 24	CENTER 21
310748	BLUE	CENTER 24	CENTER 21
310874	ORANGE	CENTER 24	CENTER 20
310913	BLUE	CENTER 24	CENTER 20
317312	BLUE	CENTER 24	CENTER 8
317427	ORANGE	CENTER 24	CENTER 8
317443	BLUE	CENTER 24	CENTER 8
320283	BLUE	CENTER 24	CENTER 21
323024	ORANGE	CENTER 24	CENTER 21
310820	ORANGE	CENTER 25	CENTER 22
310826	ORANGE	CENTER 25	CENTER 22
310850	ORANGE	CENTER 25	CENTER 22
310875	BLUE	CENTER 25	CENTER 22
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310943	ORANGE	CENTER 25	CENTER 22
310963	BLUE	CENTER 25	CENTER 22
310974	ORANGE	CENTER 25	CENTER 22
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310997	BLUE	CENTER 25	CENTER 22
311138	ORANGE	CENTER 25	CENTER 22
311145	BLUE	CENTER 25	CENTER 22
311146	BLUE	CENTER 25	CENTER 22
318358	ORANGE	CENTER 25	CENTER 22
318364	ORANGE	CENTER 25	CENTER 22
318389	BLUE	CENTER 25	CENTER 22
318541	ORANGE	CENTER 25	CENTER 22
318550	BLUE	CENTER 25	CENTER 22
318844	ORANGE	CENTER 25	CENTER 22
318848	BLUE	CENTER 25	CENTER 22
318849	ORANGE	CENTER 25	CENTER 22
320520	ORANGE	CENTER 25	CENTER 22
320521	ORANGE	CENTER 25	CENTER 22
320524	BLUE	CENTER 25	CENTER 22
320525	BLUE	CENTER 25	CENTER 22

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320526	ORANGE	CENTER 25	[redacted]
320527	BLUE	CENTER 25	[redacted]
320528	BLUE	CENTER 25	[redacted]
320529	BLUE	CENTER 25	[redacted]
320530	ORANGE	CENTER 25	[redacted]
320531	ORANGE	CENTER 25	[redacted]
328935	BLUE	CENTER 26	[redacted]
328981	BLUE	CENTER 26	[redacted]
329083	BLUE	CENTER 26	[redacted]
329168	BLUE	CENTER 26	[redacted]
329207	BLUE	CENTER 26	[redacted]
329689	ORANGE	CENTER 26	[redacted]
329703	ORANGE	CENTER 26	[redacted]
329706	ORANGE	CENTER 26	[redacted]
329709	ORANGE	CENTER 26	[redacted]
329713	ORANGE	CENTER 26	[redacted]
311157	ORANGE	MISSING	[redacted]

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From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina
Cc: adas@rti.org; Everett-Thomas, Ruth
Subject: RE: SUPPORT
Date: Tuesday, March 03, 2009 4:47:35 PM

Rose,

Congratulations! Yes, we would like to do that. Also, 2 pulse oximeters came back to us from Stanford today. Will each center that has our oximeters be sending them back to us individually? If so, please let them know that offices have moved.

It would be: Central Building, Suite 740, Jackson Memorial Hospital, 1611 NW 12 Avenue, Miami, FL 33136.

Thanks
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 03, 2009 4:26 PM
To: sduara@miami.edu; Navarrete, Cristina
Cc: adas@rti.org
Subject: SUPPORT

Hi
We enrolled our last (#1310) infant into SUPPORT late last week. We are quite interested in getting results out once the final infant reaches status. For the growth secondary study, would you like us to set up a call so we can discuss the analysis and create tables for the paper?? Let me know

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Slovis, Thomas
To: Cunningham, Meg; srhintz@stanford.edu; DBULAS@cnmc.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: RE: SUPPORT neuroimaging secondary - cranial US
Date: Tuesday, March 03, 2009 4:20:51 PM

---

the SPR meeting is the week of April 21. Let 's decide if we do a weekend plus a Monday or Friday to minimize time away from work. ESPR is first week of June. Tom

---

From: Cunningham, Meg [mcunningham@rti.org]
Sent: Tuesday, March 03, 2009 12:19 PM
To: Slovis, Thomas; srhintz@stanford.edu; DBULAS@cnmc.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; vanmeurs@leland.stanford.edu; Huitema, Carolyn Petrie
Subject: FW: SUPPORT neuroimaging secondary - cranial US

Hello All-

Please provide your availability below so we can finalize dates for these meetings. The first meeting will be held in DC and the second will be held in either NC or Detroit. For the weeks listed below, please indicate which days you would not be available to meet.

Week of:

April 13th –

April 20th –

April 27th –

May 4th –

May 11th –

May 18th –

May 25th –

June 1st –

June 8th –

June 15th –

June 22nd –

June 29th –

Thanks,
Meg

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]

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Sent: Monday, March 02, 2009 4:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz
Cc: tslovis@med.wayne.edu; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Das, Abhik; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

(b) (6) so a visit there could work as well! I could drive - Tom how about Durham over Detroit for the second visit - you love to travel dont you?
Dorothy Bulas MD

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 3/2/2009 4:09 PM
To: BULAS, DOROTHY; Susan Hintz
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US
The NC location is at RTI – Research Triangle Park (Raleigh-Durham airport is very close).

Thanks
Rose

From: BULAS, DOROTHY [mailto:DBULAS@cnmc.org]
Sent: Monday, March 02, 2009 4:05 PM
To: Susan Hintz
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; vanmeurs@stanford.edu
Subject: RE: SUPPORT neuroimaging secondary - cranial US

I think 2 days each time might work - it depends on how the images are transfered... are they still all on disc?

It would be great to start with a 2 day meeting and see how fast it goes - hopefully Tom would be up to coming to DC. the schedule is tight this spring for me.

I could get room for us at CNMC.

Let me know TOM if a trip to DC would work for you. Where in NC is your data base?

Dorothy Bulas MD

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Mon 3/2/2009 3:42 PM
To: BULAS, DOROTHY
Cc: tslovis@med.wayne.edu; petrie@rti.org; kristin zaterka; adas@rti.org; higginsr@mail.nih.gov; vanmeurs@stanford.edu; srhintz@stanford.edu
Subject: SUPPORT neuroimaging secondary - cranial US
Hi Dorothy and Tom,

It has been about 2 years since we last spoke about the "way far away" end of the SUPPORT trial - and the beginning of the central reading of the CUS for the Neuroimaging and Neurodevelopmental Secondary of that trial. Well, the time has come! The last patient was enrolled last week, so we would like to start planning and thinking about the process of the central reading.

As I explained when we first communicated about this trial, we will have 2 CUS from each of the ~500-550 patients

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that are enrolled in the neuroimaging secondary and survive to 36 weeks (one at <14 days and one at ~36 weeks PMA). We will also have an MRI at ~36 weeks for each of these patients - Pat Barnes will be central reader for those. We now are very excited to have not only 18-22 month neurodevelopmental follow-up funded, but ALSO 6-7 year follow-up. This will really be a great opportunity for us to evaluate the predictive capabilities of early and late CUS, compare with MRI, the contribution of neuroimaging to outcomes prediction in general for extremely preterm infants, and importantly to assess differences in neuroimaging abnormalities with respect to randomized interventions of oxygen saturation targets and ventilation strategies. This will be the largest preterm cohort in the world with complete, centrally-read neuroimaging and neurodevelopmental follow-up, and the only one to date with exclusively extremely preterm infants (<28 weeks). We will also be the first

When we communicated previously, it sounded like you both were in favor of at least an attempt at an "omnibus" central reading rather than getting them sent to you individually in drips and drabs. I agree in principal that this is the best approach so we can have support and helpers from the data center to help fill in the forms while you read, making things move faster. However, with ~1100 CUS, I wonder if this could really be accomplished in one single central reading event. So, my questions to you are:

1) How long will this take?: Since you have both been involved in so many trials as central readers, you will of course have a better estimate than I for how long/ how many hours and days it will take to read this many CUS. Is it reasonable to plan for 2 x central reading "events" - perhaps 2-3 days each? Contrasting with the Premie iNO central reading - a) there were fewer cranial US for PiNO than we will have for SUPPORT, b) all the PiNO CUS were not able to be read during the one central reader event, thus you both had to finish up on your own (which was probably not so easy and made things go more slowly), but c) the severity of illness for the PiNO patients was MUCH greater than for the SUPPORT patients, and I would expect that the CUS will not be as complex to read as those.

2) Location: We could do the central reading in D.C. (as we did with PiNO, as long as Dorothy can get us the space), or in North Carolina where the data center is located, or in Detroit (as long as Tom can get us the space). If we have two central reading events, we could do one close to Dorothy and one close to Tom. In any case, the data center has committed to providing "helpers" no matter where the readings occur!

3) Deadlines: We do not have all the CUS at the data center yet - some of the patients have not even reached the 36 week mark - but we have many. Also, we would love to have the readings completed by early fall 2009 (September) in order to potentially make the late breaker deadline for PAS. So, we would like to plan for a first central reading event as soon as practicable for you both. Carolyn Petrie Huitema (who helped to organize the PiNO central reading) and Kris Zaterka from RTI have been cc'd on this email and they will be helping to schedule all of this with you both.

4) Contract issues: I am not in the loop about the contracting and remuneration side of this - but Dr. Abhik Das from RTI will be the initial point person for those discussions with you both. He is also cc'd on this email.

OK - that is it for now. We are truly excited about this trial, and about the information we can provide for care providers and families. I am also very excited to continue communications with you about ideas for other analyses for these neuroimaging data we can work on together - we have a very, very rich database for these patients, and this will be an exciting and unique opportunity to learn more!

Thanks,

Susan

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304

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ph: 650-723-5711
fax: 650-725-8351

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From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Neuroimaging 6 year assessment query
Date: Tuesday, March 03, 2009 4:12:42 PM
Attachments: SUPPORT6_7yr Child Assessment Query_RB.doc

Rose
Here is our SUPPORT query
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

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Last updated February 16, 2009

In preparation for finalizing SUPPORT Neuroimaging and Neurodevelopmental Outcomes Cohort 6-7 year extended follow-up assessment and questionnaire battery, we need your help in identifying the resources and experience currently available at your site.
Please answer the following questions, complete the tables, and return to **Jamie Newman (newman@rti.org) by MARCH 3rd.**

SUPPORT Child Assessments			
Assessment Name	**Currently administer in:**		**Do not currently administer, but have access to testing materials (Y/N)**
	English	**Spanish**	
1. WISC IV			Yes
2. WISC IV - Spanish Version			No
3. NEPSY II (2008 version)			No
4. Woodcock-Johnson III – ACH • Letter/Word Identification • Calculation			May have access
5. Woodcock-Johnson III – Spanish version **(Bateria III)** - ACH • Letter/Word Identification • Calculation			No

6. If your site administers any of the above assessments in Spanish, are they administered by a :

a. Spanish speaking examiner (Y/N)

b. English speaking examiner with Spanish interpreter (Y/N)

7. Does your site currently perform the complete Movement – ABC II exam (not the checklist)? Y/N

8. If your site does perform the full Movement-ABC II (not checklist), who performs it at your site (i.e., physical therapist, occupational therapist, physician examiner, etc.)? _____

CONTINUED ON NEXT PAGE

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Last updated February 16, 2009

SUPPORT Parent Questionnaires

Questionnaire Name	Currently administer in:	
	English	**Spanish**
1. Strengths and Difficulties Questionnaire (SDQ)		
2. Questionnaire for Identifying Children with Chronic Conditions-revised (QUICCC-R)		
3. Conners Parent Rating Scale – short version	No, but may have access	
4. Social Communication Questionnaire (SCQ)		
5. PedsQL		
6, Behavior Rating Inventory of Executive Function (BRIEF-Parent)		
7. If your site administers any of the above questionnaires in Spanish, are they administered by a :		
a. Spanish speaking examiner (Y/N)		
b. English speaking examiner with Spanish interpreter (Y/N)		

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT MRI Secondary study
Date: Saturday, February 28, 2009 12:10:20 AM

Rose

Will this call just be on the HUS readings? Should we have another call with Dr Barnes about getting the MRI part - I.e. How many MRIs left (I think many many...), timeline for getting the studies read, timeline for data entry and analyses...

Thanks Rose. I am getting a bit stressed actually.

S

Sent from my iPhone

On Feb 27, 2009, at 8:44 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
>
> I think we should set up a call to discuss the details regarding the MRI secondary and potential for results for PAS 2010 – specifically comparing MRI with head US.
>
> We need to have MRI readings – RTI is labeling the currently housed MRIs and will ship to Stanford in near future
>
> US readings – we will need approximately 800-900 red by the central readers (Dorothy and Tom). We need to discuss logistics, forms, etc as well as reading days (if we have 800 at 10 min/scan – that's 133 hours!!!) – perhaps we need to carve out a couple of two day periods.
>
> Can we set up a call in the next few weeks with:
> Kris
>
> Carolyn
>
> Susan
>
> Marie
>
> Abhik
>
> Stephanie

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Neil

Rose

To get the ball rolling???
Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

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For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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From: Monica Collins
To: Monica Collins; kzaterka@rti.org; joa@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: It"s official! We got her--24.2 weeker!
Date: Friday, February 27, 2009 9:14:54 AM

It's been transmitted!

From: Monica Collins
Sent: Fri 2/27/2009 8:01 AM
To: kzaterka@rti.org; joa@rti.org; higginsr@mail.nih.gov
Subject: It's official! We got her--24.2 weeker!

I'm filling out the forms--rand #[redacted]. Will transmit eligibility form in a couple of minutes
Monica

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins; kzaterka@rti.org; joa@rti.org
Cc: nfiner@ucsd.edu; Das, Abhik; Thomas Soltau, M.D.
Subject: RE: It"s official! We got her--24.2 weeker!
Date: Friday, February 27, 2009 9:08:36 AM

Our fellow who enrolled the baby told me early the morning he was hoping this one would do it. I am copying him. Thomas: Thanks.

Congratulations and THANKS to Neil, Rose, all research nurses, PIs/coPIs and RTI staff.

This will be a very important trial.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 27, 2009 8:05 AM
To: Wally Carlo, M.D.; Monica Collins; kzaterka@rti.org; joa@rti.org
Cc: nfiner@ucsd.edu; Das, Abhik
Subject: RE: It's official! We got her--24.2 weeker!

1310th – and final infant!!!
THNASK
ROSE

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, February 27, 2009 9:04 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins; kzaterka@rti.org; joa@rti.org
Cc: nfiner@ucsd.edu; Das, Abhik
Subject: RE: It's official! We got her--24.2 weeker!

Is that the 1300th baby?

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building

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Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 27, 2009 8:03 AM
To: Monica Collins; kzaterka@rti.org; joa@rti.org
Cc: nfiner@ucsd.edu; Wally Carlo, M.D.; Das, Abhik
Subject: RE: It's official! We got her--24.2 weeker!

TERRIFIC!!!!
THANKS SO MUCH!!!
ROSE

From: Monica Collins [mailto:MCollins@peds.uab.edu]
Sent: Friday, February 27, 2009 9:02 AM
To: kzaterka@rti.org; joa@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: It's official! We got her--24.2 weeker!

I'm filling out the forms--rand #(b) (6). Will transmit eligibility form in a couple of minutes
Monica

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From: Zaterka-Baxter, Kristin
To: Hensman, Angelita; Auman, Jeanette O.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Laptook, Abbot; Auman, Jeanette O.
Subject: RE: New SUPPORT study baby enrolled 02/26/09
Date: Thursday, February 26, 2009 9:32:14 AM

Yes, both enrolled if we don't already have 1310 by the time of the delivery and an announcement has been made that accrual has ended. If that is the case, then please tell the mother that the study has met it's goal and her infants will not be enrolled.
Thanks,
Kris

From: Hensman, Angelita [mailto:AHensman@WIHRI.org]
Sent: Thursday, February 26, 2009 9:28 AM
To: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Cc: Rosemary (NIH/NICHD) [E] Higgins; Gantz, Marie; Das, Abhik; Laptook, Abbot
Subject: RE: New SUPPORT study baby enrolled 02/26/09

I have a mom with twins currently consented. Although delivery does not seem imminent she has PPROM so you never know. I am assuming they both get enrolled IF she delivers?

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, February 26, 2009 9:16 AM
To: Hensman, Angelita; Auman, Jeanette O.
Cc: Rosemary (NIH/NICHD) [E] Higgins; Gantz, Marie; Das, Abhik
Subject: RE: New SUPPORT study baby enrolled 02/26/09

Thanks Angelita!

Please submit the Supp02 asap as this is our 1309th infant enrolled and we need to have confirmation in the DMS.

Kris

From: Hensman, Angelita [mailto:AHensman@WIHRI.org]
Sent: Thursday, February 26, 2009 9:14 AM
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin
Subject: New SUPPORT study baby enrolled 02/26/09
Importance: High

(b) (6) - 26-27 6/7 wk group randomized to Early ventilation and surfactant and blue p.o group.

Angelita

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Auman, Jeanette O.
Subject: RE: MISSING DATA
Date: Tuesday, February 24, 2009 11:07:10 AM

Jenny will run the edits and missing forms reports for SUPPORT every two weeks instead of every month to help the centers keep on top of entering the data.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 24, 2009 10:24 AM
To: Gantz, Marie
Cc: Das, Abhik; Auman, Jeanette O.
Subject: RE: MISSING DATA

Fine
I don't want to be waiting for data once we are done

Thnask
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, February 24, 2009 10:23 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Auman, Jeanette O.
Subject: RE: MISSING DATA

Rose,

Abhik, Jenny and I discussed what would be the most practical way to go about doing that, and our suggestion would be for you to send out a link to the missing forms reports that are posted on the web to remind centers that we would like the data ASAP. We would send you the link when Jenny reruns the reports which should be in the first week of March. How does that sound to you?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 24, 2009 9:36 AM

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To: Gantz, Marie
Cc: Das, Abhik
Subject: RE: MISSING DATA

Can you get a list from Jenny of the missing data elements and I can start sending them to sites.

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, February 24, 2009 9:33 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: MISSING DATA

Rose,

I can't think of any data elements I think will be problematic in terms of missing data, as long as the centers fill out the SUPPORT and GDB forms promptly. They will continue to receive missing forms and batch edit reminders from Jenny. I had asked Neil the same question a couple of weeks ago to see if there was anything he could think of, but I have not heard back from him.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 23, 2009 3:20 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: MISSING DATA

Marie
Besides the usual primary outcome data that we ask for every month for SUPPORT, do you foresee other areas of missing information that we can start to get no??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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From:	Rich, Wade
To:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	FW:
Date:	Monday, February 23, 2009 4:37:23 PM
Attachments:	PAS Consent Abstract edits NF.doc

I caught a couple of mistakes if you haven't sent this out yet.
wade

From: Finer, Neil
Sent: Monday, February 23, 2009 1:17 PM
To: Rich, Wade
Subject:

A few changes

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

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Title: The Process of Antenatal Consent in a Large Multicenter Trial -

Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman BA, RN, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: Prospective research in infants involving randomization at the time of birth requires that informed consent be carried out in the antenatal period. Trial projections often fail to recognize that the number enrolled may be significantly less than those screened or consented.

Objective: This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network SUPPORT trial and better predict the true cost of recruitment into a complex trial of continuous positive airway pressure vs. intubation and surfactant in the delivery room and randomization to 2 goal ranges of saturation in the NICU.

Design/Methods: A data form was designed to quantify eligible mothers at each center, determine who approached them, how often, the duration of contact and whether the infants were eventually enrolled.

Results: 2798 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2211 were approached for informed consent. Most frequent reasons for not approaching included the presence of fetal abnormalities, active labor and language barriers. A study coordinator/research RN made 75% of all first approaches. For 77% of those approached, consent was attempted < 2 times. (Range 1-11). GA at time of screening was not different for those who consented vs those who did not. 7% of those screened were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2211 approached for consent, 1209 gave consent, 575 subsequently delivered 652 infants within study window, and 607 infants from 532 mothers were enrolled. Only 19% of those screened delivered infants who subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that are also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use $\leq$30 minutes to request consent.

Conclusions: In a complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Extrapolating these data to all 1310 infants enrolled in the SUPPORT trial suggest that > 6000 eligible women were screened. These data should assist in developing the true cost of trials requiring antenatal consent.

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: PAS Consent Abstract edits.doc
Date: Monday, February 23, 2009 1:43:27 PM
Attachments: PAS Consent Abstract edits.doc

Final abstract with committee suggestions included where practicable. (99.88% of characters allowed.)

Wade

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Title: The Process of Antenatal Consent in a Large Multicenter Trial -

Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman BA, RN, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: Prospective research in infants involving randomization at the time of birth requires that informed consent be carried out in the antenatal period. Trial projections often fail to recognize that enrollment numbers may be significantly lower than screening and consent rates..

Objective: This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network SUPPORT trial and better predict the true cost of recruitment into a complex trial of continuous positive airway pressure vs. intubation and surfactant in the delivery room and randomization to 2 goal ranges of saturation in the NICU.

Design/Methods: A data form was designed to quantify eligible mothers at each center, determine who approached them, how often, the duration of contact and whether the infants were eventually enrolled.

Results: 2798 women were identified at 18 collaborating units as being at risk for premature delivery at 24 to 27 6/7 wks GA between October 2005 and February 2009. 2211 were approached for informed consent. Most frequent reasons for not approaching included the presence of fetal abnormalities, active labor and language barriers. A study coordinator/research RN made 75% of all first approaches. For 77% of those approached, consent was attempted < 2 times. (Range 1-11). GA at time of screening was not different for those who consented vs those who did not. 7% of those screened were identified as having been approached for another maternal study and 1% for another neonatal study. Of the 2211 approached for consent, 1209 gave consent, 575 subsequently delivered 652 infants within study window, and 607 infants from 532 mothers were enrolled. Only 19% of those screened delivered infants who subsequently enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that are also NICHD Maternal Fetal Medicine network centers enrolled at a higher rate and were more likely to use <30 minutes or less to request consent.

Conclusions: In a complex interventional trial of preterm infants, nearly 5 women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Extrapolating these data to all 1310 infants enrolled in the SUPPORT trial suggest that > 6000 eligible women were screened. These data should assist in developing the true cost of trials requiring antenatal consent.

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT infant
Date: Monday, February 23, 2009 4:02:48 PM

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Monday, February 23, 2009 4:01 PM
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin
Cc: Herron, Dianne E
Subject: SUPPORT infant

We have just had a consented infant deliver and might not get the NGO2 info in until tomorrow, depending on when the infant gets into the NICU.

thanks

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (6) (pager)

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT
Date: Friday, February 20, 2009 11:39:25 AM

FYI – we got this resolved.

From: Mackinnon, Brenda [mailto:bmackinnon@tuftsmedicalcenter.org]
Sent: Friday, February 20, 2009 11:30 AM
To: Gantz, Marie
Subject: RE: SUPPORT

Yes Thank you for your help!
B

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper # (b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 20, 2009 11:25 AM
To: Mackinnon, Brenda
Subject: RE: SUPPORT

Hi Brenda,

If the infants were in room air on the day they were supposed to be tested then that's reflected on both the NG07 (question c.1.f answered 6=Weaned to room air on/before day of evaluation) and on the PHY01 (question b.8 answered 6=Weaned to room air on/before day of evaluation). Is that what you were talking about?

Thanks for your help on this!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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From: Mackinnon, Brenda [mailto:bmackinnon@tuftsmedicalcenter.org]
Sent: Friday, February 20, 2009 10:46 AM
To: Gantz, Marie
Subject: RE: SUPPORT

Marie,
That is my error they are in for GDB not PHY01. I will take care of it later today. I think, but will need to check that both were actually in room air when I went to test them. I don't remember the form by heart but I think I explain that in a comment via F5?
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper (b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 20, 2009 10:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Mackinnon, Brenda; Frantz, Ivan
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: SUPPORT

Hi Brenda,

Just to clarify, you're saying that there are PHY01 forms entered for these two infants? Jenny checked on the PHY data from Tufts (last data received on the 17th) and these two infants were not in the files, so maybe they just need to be retransmitted? As a reminder, although the physiologic definition forms are no longer transmitted to RTI for GDB infants, they are still sent for SUPPORT infants, per technical memo PHY5, attached. The two infants in question were on room air by NC at 36 weeks according to the NG07, thus the PHY01 is expected.

Thanks, and let me know if there is anything else I can do to help.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 20, 2009 9:03 AM

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To: bmackinnon@tuftsmedicalcenter.org; ifrantz@tuftsmedicalcenter.org
Cc: Das, Abhik; Gantz, Marie
Subject: Re: SUPPORT

Sometimes there is a glitch with data transfer

Marie - can you help??
Rosemary D. Higgins, MD
Program Scientist

From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Das, Abhik ; Gantz, Marie
Sent: Fri Feb 20 08:52:52 2009
Subject: RE: SUPPORT
Hi,
I found that for both of these babies the data has been collected, is in the system and has been for a while so I am not sure what the problem is but I will check with RTI.
Thanks,
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper # (b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 4:08 PM
To: Frantz, Ivan; Mackinnon, Brenda
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
Thanks for all the effort!!!!
Rose

CENTER	NETWORK	BPD_message
23	(b) (6)	PHY01 is expected based on NG07 but has not been entered
23	(b) (6)	PHY01 is expected based on NG07 but has not been entered

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Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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National Institutesof Health
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Bethesda, MD 20892
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; bmackinnon@tuftsmedicalcenter.org; ifrantz@tuftsmedicalcenter.org
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Friday, February 20, 2009 10:30:52 AM
Attachments: PHY5 20080430.pdf

Hi Brenda,

Just to clarify, you're saying that there are PHY01 forms entered for these two infants? Jenny checked on the PHY data from Tufts (last data received on the 17th) and these two infants were not in the files, so maybe they just need to be retransmitted? As a reminder, although the physiologic definition forms are no longer transmitted to RTI for GDB infants, they are still sent for SUPPORT infants, per technical memo PHY5, attached. The two infants in question were on room air by NC at 36 weeks according to the NG07, thus the PHY01 is expected.

Thanks, and let me know if there is anything else I can do to help.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 20, 2009 9:03 AM
To: bmackinnon@tuftsmedicalcenter.org; ifrantz@tuftsmedicalcenter.org
Cc: Das, Abhik; Gantz, Marie
Subject: Re: SUPPORT

Sometimes there is a glitch with data transfer

Marie - can you help??
Rosemary D. Higgins, MD
Program Scientist

From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Das, Abhik ; Gantz, Marie
Sent: Fri Feb 20 08:52:52 2009
Subject: RE: SUPPORT

Hi,
I found that for both of these babies the data has been collected, is in the system and has been for a while so I am not sure what the problem is but I will check with RTI.
Thanks,
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center

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800 Washington Street
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Boston, Ma 02111

Beeper # (b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 4:08 PM
To: Frantz, Ivan; Mackinnon, Brenda
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

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We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
Thanks for all the effort!!!!
Rose

CENTER	NETWORK	BPD_message
23	(b) (6)	PHY01 is expected based on NG07 but has not been entered
23	(b) (6)	PHY01 is expected based on NG07 but has not been entered

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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RTI INTERNATIONAL | **Memorandum**

April 30, 2008

Physiologic Definition of Bronchopulmonary Dysplasia
Physiologic Definition of BPD **Technical Memo # 5 (PHY5)**
Generic Database **Technical Memo #22 (GDB22)**
SUPPORT **Technical Memo #14 (SUP14)**
EOS **Technical Memo #07 (EOS07)**

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Physiologic Definition of Brochopulmonary Dysplasia Study

Physiologic Definition of BPD

The stand alone Physiologic Definition of Bronchopulmonary Dysplasia (BPD) study will become a subset of the GDB on May 1, 2008, per the decision of the Steering Committee at the January 2008 meeting. Data forms created for the Physiologic Definition of BPD (PHY01 and PHY02) will be used as worksheets for the revised NG07 and only entered into the data management system (DMS) when specified as necessary for individual studies.

Infants that are 36 wks PMA and eligible for challenge before May 1, 2008 should complete the current PHY01 and PHY02 forms and NG07 form version date (January 1, 2006. Infants 36 wks PMA and eligible for challenge after May 1, 2008 are no longer required to enter the PHY01 and PHY02 forms and should complete the NG07 form version date May 1, 2008.

The following questions have been added on the May 1, 2008 version of the GDB study Respiratory Support form (NG07) to document whether or not an infant has BPD using the physiologic definition of BPD.

1. Is the infant eligible for the physiologic evaluation? Y N
If YES to question C.1
a. Was the evaluation performed? Y N
If YES to question C.1.a
b. Date of evaluation __ __ / __ __ / __ __ __ __ (Month / Day / Year)
c. Actual FiO2 being delivered at time of challenge For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field. __ . __ __
d. If on nasal cannula at time of challenge, record flow rate __ . __ __ __ *LPM*
e. Did the patient pass the evaluation? Y N
If NO to question C.1.a
f. If patient was eligible and evaluation not done, code reason.

1= Increased FiO2
2= Increased respiratory support (cpap or vent)
3= Instability (including Surgery/Sepsis)
4 = Parent/Physician Refusal
6 = Weaned to room air on/before day of evaluation
9 = Other- explain

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The physiologic evaluation for BPD will be completed on eligible SUPPORT study infants. The results of the evaluation will be recorded on the revised NG07. In addition to the NG07 data, the PHY01 and PHY02 forms will continue to be entered into the DMS for SUPPORT patients whenever section **C. Physiologic Evaluation** on the new NG07 is required to be completed.

EOS Study

Infants enrolled in the EOS study, outside of the GDB criteria will NOT have the physiologic definition of BPD performed for the purposes of the EOS study. Infants outside of the GDB criteria (a gestational age greater than or equal to 29 week and weighing 1001-1500g) will continue to have other relevant GDB data collected.

Cc. Rosemary Higgins, MD

Enclosed:

NG07 (May 1, 2008)
GDB Manual (May 1, 2008)

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From: Wally Carlo, M.D.
To: Neil Finer" <
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Michelle Walsh; Bradley.yoder@hsc.utah.edu; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Nancy Newman; Abhik Das
Subject: FW: *******PAS Consent LATE BREAKER Abstract*******
Date: Thursday, February 19, 2009 8:41:21 PM
Attachments: PAS Consent Abstract.doc

Neil:

Here are my suggestions.

Great job!

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 19, 2009 1:53 PM
To: Finer, Neil; Wally Carlo, M.D.; mcw3@cwru.edu; Bradley Yoder; Roger Faix; Laptook, Abbot; Kurt Schibler; nancy newman; Rich, Wade; Gantz, Marie; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: *******PAS Consent LATE BREAKER Abstract*******

To the SUPPORT SUBCOMMITTEE - Please review and send comments back to Wade and Neil by Monday February 23.

This is a planned LATE BREAKER for the PAS meeting.

Thanks
Rose

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Title: The Process of Antenatal Consent in a Large Multicenter Trial -

Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman RNC, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: R~~**Prospective** r~~esearch in newborn infants that involves randomization at the time of birth usually~~,~~ requires that the process of informed consent be carried out in the antenatal period. (All RCTs are prospective but some may not require consent)

Objective: This study was designed to quantify the time and effort involved in enrolling infants into the recently completed NICHD Neonatal Research Network SUPPORT trial, a complex 2x2 factorial randomized controlled trial of continuous positive airway pressure vs. intubation and surfactant in the delivery room and randomization to two levels of oxygen exposure.

Design/Methods: A data collection form was designed to quantify the true numbers of eligible mothers at each center~~,~~ ~~—~~and to determine who approached them, how often,~~ for~~ how long, and whether the infants were eventually enrolled.

Results: 2850 women were identified as being eligible in the 17 collaborating units as being at risk to deliver in the study window between October 2005 and February 2009, of whom 2300 were approached for informed consent. Most frequent reasons for not approaching included fetal abnormalities and active labor and language. Three fourths of first attempts were made by a study coordinator/research RN. 77% of mothers were approached 2 or fewer times~~.~~ (Range 1-11). Screening was evenly distributed over gestational window. GA at time of screening was not different for those who consented vs those who did not. Only 5% of screened subjects were identified as being in another maternal study~~,~~ ~~—~~and 8% in a neonatal study. Of the 2300 women approached for consent, 1225 provided consent, 1000 subsequently delivered in the study window and 610 infants were enrolled. Thus the enrollment rate was 21% of eligible women. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.02$). Centers who are also MFM centers (criteria for being an MFM center) approach more women, get more consults, enroll at a higher rate, and are more likely to use < 30 minutes.

Conclusions: In a complex interventional trial of sick preterm infants, five women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Extrapolating these~~is~~ data to the entire 1310 infants enrolled in the SUPPORT trial would suggest that over 6100 eligible women were screened. These~~his~~ data should assist in developing the true effort and cost of ~~trials requiring~~ antenatal consent for such trials.

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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Melissa Leps; Pablo Sanchez; Roy Heyne
Cc: Abhik Das; Marie Gantz
Subject: Re: SUPPORT
Date: Thursday, February 19, 2009 6:40:15 PM

Rose,
I'm reporting on the ROP exams:
(b) (6) Is still in the NICU but ROP exams have reached status. The data is keyed and transmitted.
(b) (6) ROP exams have reached status, data is keyed and transmitted.
(b) (6) We know the baby didn't have ROP but we need to locate the form to key in the data.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/18/2009 1:46 PM >>>
Hi,

We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.

Thanks for all the effort!!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

4

(b) (6)

No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been

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reached.

4

(b) (6)

No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.

CENTER

NETWORK

FU_message

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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higginsr@mail.nih.gov

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From:	Walsh, Michele
To:	Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally_Carlo_M.D.; mcw3@cwru.edu; Bradley Yoder; Roger Faix; Laptook, Abbot; Kurt Schibler; nancy newman; Rich, Wade; Gantz, Marie; Das, Abhik
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject:	RE: *******PAS Consent LATE BREAKER Abstract*******
Date:	Thursday, February 19, 2009 5:50:59 PM
Attachments:	PAS Consent Abstract.doc

Some comments- looks good!

Michele Walsh
beeper(b) (6)
Ph 216 844 3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 19, 2009 2:53 PM
To: Finer, Neil; Wally_Carlo_M.D.; mcw3@cwru.edu; Bradley Yoder; Roger Faix; Laptook, Abbot; Kurt Schibler; nancy newman; Rich, Wade; Gantz, Marie; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: *******PAS Consent LATE BREAKER Abstract*******

To the SUPPORT SUBCOMMITTEE - Please review and send comments back to Wade and Neil by Monday February 23.

This is a planned LATE BREAKER for the PAS meeting.

Thanks
Rose

Visit us at www.UHhospitals.org.

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Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman RNC, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: Prospective research in newborn infants that involves randomization at the time of birth, requires that the process of informed consent be carried out in the antenatal period.

Objective: This study was designed to quantify the time and effort involved in enrolling infants into the recently completed NICHD Neonatal Research Network SUPPORT trial, a complex 2x2 factorial randomized controlled trial of continuous positive airway pressure vs. intubation and surfactant in the delivery room and randomization to two levels of oxygen exposure.

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Comment [mw1]: You mean did not speak English?

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Formatted: Highlight

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: PAS Consent Abstract MGedits.docx
Date: Thursday, February 19, 2009 3:48:42 PM
Attachments: PAS Consent Abstract MGedits.docx

Hi rose,

Here is the corrected version with true data from Marie and a couple of statements that turned out to be untrue removed.

Wade

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Title: The Process of Antenatal Consent in a Large Multicenter Trial -

Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman RNC, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: Prospective research in newborn infants that involves randomization at the time of birth requires that the process of informed consent be carried out in the antenatal period.

Objective: This study was designed to quantify the time and effort involved in enrolling infants into the NICHD Neonatal Research Network SUPPORT trial, a complex 2x2 factorial randomized controlled trial of continuous positive airway pressure vs. intubation and surfactant in the delivery room and randomization to two levels of oxygen exposure.

Design/Methods: A data collection form was designed to quantify the true number of eligible mothers at each center and to determine who approached them, how often, for how long and whether the infants were eventually enrolled.

Results: 2798 women were identified at the 18 collaborating units as being at risk to deliver in the study window between October 2005 and February 2009, of whom 2211 were approached for informed consent. Most frequent reasons for not approaching included fetal abnormalities, active labor and translation issues. . Three fourths of attempts to obtain consent were made by a study coordinator/research RN. For 77% of mothers approached, consent was attempted 2 or fewer times. (Range 1-11). GA at time of screening was not different for those who consented vs those who did not. Only 7% of screened subjects were identified as being approached for another maternal study, and 1% were approached for another neonatal study. Of the 2211 women approached for consent, 1209 provided consent, 575 subsequently delivered 652 infants in the study window and 607 infants from 532 mothers were enrolled. Thus, only 19% of women who were screened delivered infants who were enrolled in the study. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.0001$). Centers that are also MFM centers enroll at a higher rate, and are more likely to use < 30 minutes.

Conclusions: In a complex interventional trial of sick preterm infants, nearly five women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Extrapolating this data to the entire 1310 infants enrolled in the SUPPORT trial would suggest that over 6000 eligible women were screened. These data should assist in developing the true cost of trials requiring antenatal consent.

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Antenatal Consent
Date: Thursday, February 19, 2009 2:33:38 PM
Attachments: PAS Consent Abstract.doc

Here is the current version of the abstract.
wade

-----Original Message-----
From: Rich, Wade
Sent: Wednesday, February 18, 2009 9:40 AM
To: 'Gantz, Marie'
Subject: RE: Antenatal Consent

I think these are the pertinent ones. I have attached a draft of the abstract with made up numbers so you can double check that all of these statements can be answered using what is attached.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, February 18, 2009 7:50 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

Hi Wade,

I'll look into your question. Are we on for the abstract? If so, would you send me either a list of the tables you want me to rerun, or even better, copies of the old tables you want me to reproduce? FYI, we're only 10 infants away from completing SUPPORT enrollment (we're at 1300).

Thanks!
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Wednesday, February 18, 2009 10:42 AM
To: Gantz, Marie
Subject: RE: Antenatal Consent

Hi Marie,
One of the things that stands out to me if the fact that we did not approach infants until they were 24+ wks. Almost no one approached 23 week moms. Would we be able to look at the number of infants who were born at 24wks (by day) compared to the number that were approached? I think it may be an important piece of information for trials of this type if we are missing the youngest kids. It would certainly be a strong argument for waiver of consent.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]

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Sent: Friday, March 09, 2007 12:55 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

Attached are two documents. One contains the first and last birth dates and record creation dates for each center from the ANT01. In some cases, there is quite a bit of difference between the birth dates and record dates, but I looked at the data and they all appear to be legitimate. It looks like some centers just didn't have the chance to enter data in the DMS until well after data collection began.

The other document contains cross-tabulations of performing a consult vs. obtaining consent. Chi-square tests are given for each cross-tab.
The chi-square test is a test of independence, so if the p-value is significant it indicates that the consult and consent are not independent of one another. I have added some notes and (fairly hideous) color-coding to help you interpret the document. Let me know if you have any questions. I included tests for all centers together, all centers excluding those where a consult is always performed, and each center individually. By the way, if you are viewing the document on your computer screen, make sure that your page headers are visible. That's where the titles are (so you can tell which center(s) you're looking at).

Have a great weekend!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Friday, March 09, 2007 10:46 AM
To: Gantz, Marie
Subject: RE: Antenatal Consent

First and last birth date and first and last record creation date would be awesome.
There is also a statistic that Neil mentioned that I think would be helpful. I am not sure how to run it, but I would like to know the effect of performing an antenatal consult on obtaining a consent. It would be interesting to look at it by center, to see if the practice of doing consults effects
consent rates. Much to my surprise, only 2/3rd of the
Ante02s indicate a consult for a group of babies most of whom are being
seen at 24-26 weeks.

Wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, March 09, 2007 7:10 AM
To: Wade Rich
Subject: RE: Antenatal Consent

I think that should be the statisticians' motto! Yes, everything ends up being more complicated than you ever expected. Oh well, it keeps us busy.

Let's see... the only dates on the forms are the last date eligible for the moms and the birthdates for the infants. We also have the record creation dates for the entries. The record creation dates would reflect the start dates for the

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centers, but also depend on how quickly the centers enter the data after it's collected. I can give you the first and last birth date, first and last record creation date, or both for each center. Does that help? I know from past experience that going this route is easier and more accurate than trying to look at something like IRB approval dates. What do you think?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Friday, March 09, 2007 10:06 AM
To: Gantz, Marie
Subject: RE: Antenatal Consent

Hi Marie,
Would it be possible to get Antenatal Consent start-months for all the centers? We (UCSD) are about 18 months out, but we started earlier than most. And I obviously need to account for the 4 centers who are out in 4/06, and how many months the 4 new ones have been
enrolling.
It all seems so easy when you start...
Wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, March 08, 2007 5:17 AM
To: Wade Rich
Subject: RE: Antenatal Consent

Actually, I can also get you the total number of babies that were delivered in the window by mothers who were screened. Is that what you need?

Marie

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 6:19 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

That gives us a numerator (# of enrolled babies), but the denominator(total # of babies delivered), still escapes us. Right?

Wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, March 07, 2007 2:53 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

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I just realized I was wrong -- the ANT01 does link the antenatal consent mothers to the SUPPORT babies. I will get you the numbers you asked for tomorrow morning.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 12:45 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

That is certainly a good option if it is possible.
Tx.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, March 07, 2007 9:38 AM
To: Wade Rich
Cc: Neil Finer
Subject: RE: Antenatal Consent

Hi Wade,

Unfortunately, there is no ID to link the records from SUPPORT to the Antenatal consent data (SUPPORT uses the usual network ID, but Antenatal consent has a separate "screening ID"). I think the best I could do is to look at the number of infants (and number of moms) enrolled at each center since they started participating in the Antenatal consent secondary.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 12:33 PM
To: Gantz, Marie
Cc: Neil Finer
Subject: RE: Antenatal Consent

Marie,

Do we have a way of knowing how many babies these 1249 moms had, and of those how many were enrolled ?

Wade

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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, March 06, 2007 3:37 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

Here are the frequencies from ANT02, totals and by center. I also printed out the "other" reasons that mothers were not approached for consent, by center. Let me know what else you need.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, March 01, 2007 4:22 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

Well, first blush I need to look at the answers to Ante02. Is it possible to just get them as percentages as a first look? I would like to look at that overall and by center, to see if someone is being more successful and why.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, March 01, 2007 1:09 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

Just let me know what you need, and I will get it for you. Call or email me -- whatever works best for you.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, March 01, 2007 3:50 PM
To: Gantz, Marie
Subject: Antenatal Consent

Hi Marie,
I need to start gathering data for my talk in April to ACRP re:
Antenatal Consent. I am not doing a final obviously, just presenting what we are learning so far. I know you guys are "pre-SPR", so let me know when I can get a word in edgewise and can get the data we have so far.

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Tx.
wade

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Title: The Process of Antenatal Consent in a Large Multicenter Trial -

Wade Rich BSHS,RRT,CCRC, Kathy Auten MSHS, Marie Gantz PhD, Ellen Hale RN,BS, Angelita Hensman RNC, Nancy Newman RNC, Nancy Peters RN CCRP, Neil Finer, MD for the NICHD Neonatal Research Network[1]Pediatrics/Neonatology, UCSD Medical Center, San Diego, CA, United States.

Background: Prospective: ~~r~~Research in newborn infants that involves randomization at the time of birth, requires that the process of informed consent be carried out in the antenatal period.

Objective: This study was designed to quantify the time and effort involved in enrolling infants at 24- 27 6/7 weeks gestational age into the recently completed NICHD Neonatal Research Network SUPPORT trial, a complex 2x2 factorial randomized controlled trial of continuous positive airway pressure vs. intubation and surfactant ~~in the~~ following delivery room stabilization and randomization to two levels of oxygen exposure.

Design/Methods: A data collection form was designed to quantify the true numbers of eligible mothers at each center, ~~-~~and to determine who approached them, how often, for how long, and whether the infants were eventually enrolled.

Results: 2850 women were identified as being eligible in the 17 collaborating units as being at risk to deliver in the study window between October 2005 and February 2009, of whom 2300 were approached for informed consent. Most frequent reasons for not approaching included fetal abnormalities, ~~and~~ active labor, and language(?unavailability of translation services??). Three fourths of first attempts were made by a study coordinator/research RN. 77% of mothers were approached 2 or fewer times. (Range 1-11). Screening was evenly distributed over gestational age (GA) window. GA at time of screening was not different for those who consented vs those who did not. Only 5% of screened subjects were identified as being in another maternal study, and 8% in a neonatal study. Of the 2300 women approached for consent, 1225 provided consent, 1000 subsequently delivered in the study window and 610 infants were enrolled. Thus the enrollment rate was 21% of eligible women. There was a significant relationship between performing a neonatal consult and obtaining consent ($p<.02$). Centers who are also MFM centers approach more women, get more consults, enroll at a higher rate, and are more likely to use < 30 minutes.

Conclusions: In a complex interventional trial of sick preterm infants, five women were identified as likely to deliver a baby in the window for every infant enrolled in the trial. Extrapolating this data to the entire 1310 infants enrolled in the SUPPORT trial would suggest that over 6100 eligible women were screened. This data should assist in developing the true cost of trials requiring antenatal consent.

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From: Finer, Neil
To: "Frantz, Ivan"; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Subject: RE: Support
Date: Thursday, February 19, 2009 12:35:44 PM

Only the infant with the omphalocele is ineligible.
Good luck – these could be close to the last infants enrolled.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Friday, February 13, 2009 6:15 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Subject: Support

I have another eligibility question. We have a 27 5/7 mother (b) (6) (b) (6) Do we consent them and enroll (b) (6) ineligible?

Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

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From: Bonnie Siner
To: mcw3@cwru.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT
Date: Thursday, February 19, 2009 10:34:53 AM

Rose,
Please forward these edits to me also since I do the follow-up.
Now, this patient ... has been a no show x6 in ophthalmology per my most recent contact with them this morning.
We are attempting to contact the mother and will offer an incentive.

Bonnie Siner

From: nancy newman [mailto:nxs5@case.edu]
Sent: Thursday, February 19, 2009 10:29 AM
To: 'Bonnie Siner'
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 2:41 PM
To: mcw3@cwru.edu; nxs5@cwru.edu
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing. This is absolutely spectacular given your outstanding recruitment!!!!!

Thanks for all the effort!!!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 18, 2009 7:36:25 PM

I am a research nurse that works with Monica. She is away this week. The infant with GDB (b) (6) has not met the criteria for final acute status (not yet mature or in zone 3 for 2 exams). The infant had one exam on DOL 46 that showed immature vessels in zone 2 ou. The second exam showed immature vessels zone 3ou. The infant is beyond 55 weeks PMA and is to be scheduled for an exam sometime between May and September. We were waiting for the results of this exam to determine status. Let us know what you would like us to do.
Thank You,
JoAnn Poulsen

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
>
> Thanks for all the effort!!!!
> Rose

CENTER	NETWORK	FU_message
13	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed
13	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed

CENTER	NETWORK	ROP_message
13	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Dusick, Anna M.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, February 18, 2009 4:57:23 PM

?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 2:57 PM
To: Wally_Carlo_M.D.; ambal@uab.edu; mperalta@peds.uab.edu; scosby@peds.uab.edu; mcollins@peds.uab.edu; Vivien Phillips
Cc: Gantz, Marie; Dusick, Anna M.
Subject: SUPPORT

Hi,
We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
This is absolutely spectacular given your outstanding recruitment!!!!!
Thanks for all the effort!!!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Wednesday, February 18, 2009 4:12:08 PM

If ROP is still pending when the FU window opens, then the center gets reminded to try to obtain the ROP outcome during follow-up. The FU window is calculated based on adjusted age.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
[redacted]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 4:06 PM
To: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Gantz, Marie
Cc: Das, Abhik
Subject: FW: SUPPORT

The ROP outcomes are still listed as pending at 18 months chronologic or corrected age??

From: Hensman, Angelita [mailto:AHensman@WIHRI.org]
Sent: Wednesday, February 18, 2009 3:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; Laptook, Abbot; Vohr, Betty; Ventura, Suzy
Subject: RE: SUPPORT

Just wanted to clarify the Follow up windows for the ROP outcomes. We are figuring out the 18 month follow up window dates based on the "Chronological" age. I am told the Follow up (18 month) appointments are made based on the infant's "Corrected" age. This means some of the Follow up appointments are 3-4 months later but we get queried on them based on the Chronological age birth. Which dates should we be using?

Thanks

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 18, 2009 2:55 PM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Ventura, Suzy
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing some SUPPORT Primary Outcomes. Please let us know how you are doing.
This is absolutely spectacular given your outstanding recruitment!!!!!
Thanks for all the effort!!!!
Rose

CENTER	NETWORK	ROP_message
14	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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301-496-5575
301-496-3790 (FAX)
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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Wednesday, February 18, 2009 1:47:20 PM
Attachments: Infants with missing outcomes 02-18-09.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
4		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
13		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support enrollment
Date: Sunday, February 15, 2009 8:22:54 AM

I don't think I heard about those patients. I'll look out for them!
That would make 1298, getting closer!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, February 15, 2009 8:21 AM
To: Auman, Jeanette O.
Subject: Re: support enrollment

Great - Tufts has a (b) (6) [redacted] that they were consenting Friday!!
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Auman, Jeanette O. <joa@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sun Feb 15 08:18:28 2009
Subject: RE: support enrollment

Email works great, I have it on all the time. We are up to 1296 now.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, February 15, 2009 8:15 AM
To: Auman, Jeanette O.
Subject: Re: support enrollment

Jenny
Is email notification as good as the dial in number? If not, let me know and I can send folks a note
What are we up to??
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Auman, Jeanette O. <joa@rti.org>
To: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Melissa Leps <Melissa.Leps@UTSouthwestern.edu>; Nancy Miller <Nancy.Miller@UTSouthwestern.edu>
Sent: Sun Feb 15 08:11:41 2009
Subject: RE: support enrollment

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Thanks!

-----Original Message-----
From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]
Sent: Sunday, February 15, 2009 12:45 AM
To: Auman, Jeanette O.
Cc: rose higgins; Zaterka-Baxter, Kristin; Melissa Leps; Nancy Miller
Subject: support enrollment

Jenny--we just enrolled another infant on SUPPORT-25 weeks, randomized to CPAP arm--pablo

Pablo J. Sanchez, M.D.
Professor of Pediatrics
University of Texas Southwestern Medical Center
Dept. of Pediatrics
5323 Harry Hines Blvd. (Room E3.508)
Dallas, TX 75390-9063
214-648-3753
214-648-2481 (fax)
972-206(b) (6) (beeper)
214-621(b) (6)(cell)
Pablo.Sanchez@UTSouthwestern.edu

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Antenatal Consent
Date: Friday, February 13, 2009 1:49:59 PM

Hi Rose,

Neil asked if I would do a late-breaker abstract for the Antenatal Consent study, since it is not a secondary of SUPPORT as such. From whom do I need to get permission if such can be granted?

PS. Marie is up for it since she has already made the tables and just needs to re-run them.

Wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 13, 2009 10:45 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

OK, sounds good. I'm about to take off for the day (b) (6) (b) (6) but let's talk next week.

Have a good weekend!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Friday, February 13, 2009 1:44 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

For an abstract I think what we did before is plenty. So it should just be rerunning them. It would be awesome to wait until the final kid is enrolled, but that may be too much to ask. In any case we will have 2800 eligibles.

Wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 13, 2009 10:42 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

If it's basically what we did before then it should be doable because it's just a matter of rerunning existing programs. And yes, (b) (6) ☺

Marie

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From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Friday, February 13, 2009 1:40 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

(b) (6) [redacted]? The good news is that you already did all of the tables once. We just need to put in the new numbers.
wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 13, 2009 10:31 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

When is it due?

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Friday, February 13, 2009 1:31 PM
To: Gantz, Marie
Subject: Antenatal Consent

Hi Marie,
Are you up for trying to squeeze out a Late-Breaker abstract of the Antenatal Consent trial if Rose will let us?
wade

Wade Rich BSHS, RRT, CCRC
Research Coordinator - Neonatology
UCSD Medical Center
402 Dickinson St. Ste 1-140
San Diego, CA 92103-8774
Ph. 619-543-5375
FAX 619-543-3812

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; nfiner@ucsd.edu
Cc: Zaterka-Baxter, Kristin; Gantz, Marie
Subject: Re: Support
Date: Friday, February 13, 2009 9:36:01 AM

Agreed. Eligible babies from a multiple pregnancy can be enrolled.

Abhik Das
Senior Research Statistician
RTI International

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 13, 2009 09:20 AM Eastern Standard Time
To: ifrantz@tuftsmedicalcenter.org; nfiner@ucsd.edu; Das, Abhik
Cc: Zaterka-Baxter, Kristin
Subject: Re: Support

The (b) (6) are eligible and may be enrolled.
Let ius know if you have other questions

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Frantz, Ivan
To: nfiner@ucsd.edu ; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Sent: Fri Feb 13 09:15:25 2009
Subject: Support

I have another eligibility question. We have a 27 5/7 mother (b) (6). Do we consent them and enroll (b) (6) ineligible?

Ivan D. Frantz, III, M.D.

Professor of Pediatrics

Tufts University School of Medicine

Tufts Medical Center Box 44

800 Washington St.

Boston, MA 02111

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617 636 5322

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From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; Kristin Zaterka-Baxter; Nancy Miller; Pablo Sanchez
Subject: Adverse Event on SUPPORT infant
Date: Wednesday, February 11, 2009 5:07:49 PM

This is notification of an adverse event on NN#(b) (6) (b) (6) [redacted]

The adverse event will be written up and forwarded as soon as possible.

On a lighter note, I am very glad to say that this infant has now(b) (6) [redacted] :)

Thank you

Missy Leps, RN
Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206.(b) (6)
fax: 214.648.2481

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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Melissa Leps; Pablo Sanchez
Subject: RE: Adverse Event 2/5/09
Date: Tuesday, February 10, 2009 3:56:48 PM

Rose,
No, we haven't sent it yet. We'll fax the MedWatch after it's approved by Pablo. He's been on service.
Thanks,
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/10/2009 11:01 AM >>>
Did this get faxed to us? It may have gotten lost.

Thanks
Rose

From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]
Sent: Friday, February 06, 2009 11:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Melissa Leps; Nancy Miller
Subject: Re: Adverse Event 2/5/09

no--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/6/09 3:45 PM >>>

Is this felt to be study related?
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; Kristin Zaterka-Baxter ; Nancy Miller ; Pablo Sanchez
Sent: Fri Feb 06 14:57:31 2009
Subject: Adverse Event 2/5/09

This is notification of another adverse event on SUPPORT patient (b) (6) This infant experienced (b) (6) This event was previously reported.

(b) (6)

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(b) (6)
[redacted]

If additional info is needed, please let me know.

Thank you--

Missy Leps, RN

Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206(b) (6)
fax: 214.648.2481

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From: Finer, Neil
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade; Gantz, Marie
Subject: RE: question re: SUPPORT
Date: Friday, February 06, 2009 12:43:16 PM

Hi Kris

I think that the approach that the centers are taking is quite appropriate – I would continue to consent and indicate that if the study closes before their delivery, their child will not be enrolled. If we enroll 2-5 extra infants, that is not a problem, but because the SUPPORT consent is such a good tocolytic, I would keep trying to get consent. If we have some consented Moms that do not deliver but we are counting on that delivery to help enrollment, we will probably be waiting a while.

Thanks for everyone's great continuing efforts

Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, February 03, 2009 2:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik; Rich, Wade; Gantz, Marie
Subject: FW: question re: SUPPORT

Hi,

Please see the email string below about consenting mom's in support given we are close to accrual goal; please comment on the centers' approaches if needed. I'm not sure we've had a discussion on a uniformed approach (or if it is needed).

Thanks and please note I've attached the original email to the string below; it was not included with the center responses.

Kris

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Tuesday, February 03, 2009 4:38 PM
To: Monica Collins; Michelle Tidwell; Barbara Alexander
Cc: Estelle Fischer; Jody Shively; Kurt Schibler; nxs5@cwru.edu; kimberley.fisher@duke.edu; grisbyca@email.uc.edu; Lenora Jackson; Karen.Osborne@hsc.utah.edu; dhwilson@iupui.edu; ldw@iupui.edu; mball@leland.stanford.edu; rbara@med.wayne.edu; ellen_hale@oz.ped.emory.edu; Shirley Cosby; Vivien Phillips; Auman, Jeanette O.; Zaterka-Baxter, Kristin; cbackstrom@salud.unm.edu; BMackinnon@tufts-nemc.org; wrich@ucsd.edu; Georgia.E.McDavid@uth.tmc.edu; Nancy.Miller@UTSouthwestern.edu; ahensman@wihri.org; elaine.romano@yale.edu; monica.konstantino@yale.edu
Subject: RE: question re: SUPPORT

Same here at Iowa.
Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (319) 356(b) ask for pager (b)

"Far and away the best prize that life offers is the chance to work hard at work worth doing." Theodore Roosevelt

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From: Monica Collins [mailto:MCollins@peds.uab.edu]

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Sent: Tuesday, February 03, 2009 2:14 PM
To: Michelle Tidwell; Barbara Alexander
Cc: Estelle Fischer; Jody Shively; Kurt Schibler; nxs5@cwru.edu; kimberley.fisher@duke.edu; grisbyca@email.uc.edu; Lenora Jackson; Karen.Osborne@hsc.utah.edu; dhwilson@iupui.edu; ldw@iupui.edu; mbball@leland.stanford.edu; rbara@med.wayne.edu; ellen_hale@oz.ped.emory.edu; Shirley Cosby; Vivien Phillips; joa@rti.org; kzaterka@rti.org; cbackstrom@salud.unm.edu; BMackinnon@tufts-nemc.org; wrich@ucsd.edu; Johnson, Karen; Georgia.E.McDavid@uth.tmc.edu; Nancy.Miller@UTSouthwestern.edu; ahensman@wihri.org; elaine.romano@yale.edu; monica.konstantino@yale.edu
Subject: RE: question re: SUPPORT

Michelle's response is the same as ours at UAB

From: Michelle Tidwell [mailto:Michelle_Tidwell@oz.ped.emory.edu]
Sent: Tue 2/3/2009 1:49 PM
To: Barbara Alexander
Cc: Estelle Fischer; Jody Shively; Kurt Schibler; nxs5@cwru.edu; kimberley.fisher@duke.edu; grisbyca@email.uc.edu; Lenora Jackson; Karen.Osborne@hsc.utah.edu; dhwilson@iupui.edu; ldw@iupui.edu; mbball@leland.stanford.edu; rbara@med.wayne.edu; ellen_hale@oz.ped.emory.edu; Monica Collins; Shirley Cosby; Vivien Phillips; joa@rti.org; kzaterka@rti.org; cbackstrom@salud.unm.edu; BMackinnon@tufts-nemc.org; wrich@ucsd.edu; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu; Nancy.Miller@UTSouthwestern.edu; ahensman@wihri.org; elaine.romano@yale.edu; monica.konstantino@yale.edu
Subject: Re: question re: SUPPORT

Our plan here at Emory is to let moms know that if they consent and we reach our enrollment goal prior to their delivery they will not be enrolled. Our consent states that our enrollment goal is around 1300. We will inform moms that we are close to the goal now.

Michelle

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899-(b) pager

To all:

While consenting prenatally for SUPPORT, should we be telling the participants that its possible that they consent and deliver but wouldn't get enrolled?

For example: we consent MS Jones 2/3 she is 24 weeks , on 2/6 we reach 1310-- Ms Jones delivers the next day(2/7) still in the window, but would not get enrolled. Should we be letting the particpates know this during the consenting process?

Thanks, just wondered what everyone was doing for this

Barb Alexander RN

Barbara Alexander RN
Clinical Research Coordinator
Division of Neonatology
Cincinnati Children's Hospital Medical Center office 513.803.0954 fax 513.803.0969

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From: Zaterka-Baxter, Kristin
To: Monica Konstantino; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support patient
Date: Wednesday, February 04, 2009 12:35:31 PM

Thanks Monica, can you please confirm the death was not thought to be related to study.
Thanks,
Kris

-----Original Message-----
From: Monica Konstantino [mailto:monica.konstantino@yale.edu]
Sent: Wednesday, February 04, 2009 12:27 PM
To: Higgins, Rosemary (NIH/NICHD); Zaterka-Baxter, Kristin
Subject: support patient

Hi, (b) (6) died today. She was born (b) (6) 24+2wks, 420gms randomized to early surf. The baby (b) (6)

(b) (6) I am faxing to you both the medwatch. thanks,
Monica

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From: Maureen Hack
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: srhintz@stanford.edu
Subject: Re: SUPPORT FU ancillary
Date: Tuesday, February 03, 2009 3:58:46 PM

Rose, I think that this is a very worthwhile project but because it comes from our center I am a little biased and thus did not reply. We have started looking at the issue of sleep apnea in our current 6 year ELBW cohort of which I am a co PI with our neuropsychologist Dr Taylor who is PI. It is not clear to me whether the whole Support cohort is also funded for a pulmonary school age follow and how this is going to be coordinated with the neuroimaging cohort. It has become difficult to follow kids at school age in general as most mothers work now days and to have the families come in twice, once for the neruoimaging study and once for the pulmonary study is going to be difficult, Maureen

At 09:01 AM 2/3/2009, you wrote:
>Hi,
>I had previously sent this secondary study for input and have
>obtained comments from many of you. If you have additional input
>for comments, please send them to me by today so that I can get back
>to Drs. Hibbs and Walsh. The comments thus far and fairly
>enthusiastic with changes requested for the years of FU and
>addressing power issues if this applies only to the neuroimaging cohort.
>
>Thanks
>Rose
>
>Rosemary D. Higgins, MD
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
>Center for Developmental Biology and Perinatal Medicine
>Eunice Kennedy Shriver National Institute of Child Health and Human
>Development
>National Institutesof Health
>6100 Executive Blvd., Room 4B03
>MSC 7510
>Bethesda, MD 20892
>For overnight delivery use Rockville, MD 20592
>301-496-5575
>301-496-3790 (FAX)
>higginsr@mail.nih.gov
>
>

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From: Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: srhintz@stanford.edu
Subject: Re: SUPPORT FU ancillary
Date: Tuesday, February 03, 2009 2:35:33 PM

Hi Rose,
The SDB protocol is certainly interesting. Given the length of the follow-up visit, I would be more enthusiastic if it was an opt in/out telephone questionnaire administered by the proposing site.
Thanks,
Beth

Hi,

I had previously sent this secondary study for input and have obtained comments from many of you. If you have additional input for comments, please send them to me by today so that I can get back to Drs. Hibbs and Walsh. The comments thus far and fairly enthusiastic with changes requested for the years of FU and addressing power issues if this applies only to the neuroimaging cohort.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

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higginsr@mail.nih.gov

Content-Type: application/msword;
name="Critique of SDB Protocol.doc"
Content-Description: Critique of SDB Protocol.doc
Content-Disposition: attachment;
filename="Critique of SDB Protocol.doc"

Attachment converted: Macintosh HD:Critique of SDB Protocol.doc
(WDBN/«IC») (004BB50A)
Content-Type: application/msword;
name="SDB ancillary study proposal 11 13 08 (5).doc"
Content-Description: SDB ancillary study proposal 11 13 08 (5).doc
Content-Disposition: attachment;
filename="SDB ancillary study proposal 11 13 08 (5).doc"

Attachment converted: Macintosh HD:SDB ancillary study #4BB50B.doc
(WDBN/«IC») (004BB50B)

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Bethany Ball
Division of Neonatal and Developmental Medicine
650.725.8342

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From: Susan Hintz
To: Newman, Jamie
Cc: hammond@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support request to sites for info
Date: Monday, February 02, 2009 4:22:41 PM

Hi all,

Rose recently got input from another psychologist at NICHD, and I think her response leaves the question still open about whether a Spanish-speaking examiner is REALLY needed for these tests -

Rose - am I interpreting your emails correctly on this point? Obviously, it will be best to have Spanish speaking psychologist examiners, and I think that should be the primary option we want to recommend to the sites. There is a good deal of lead time for the sites to set it up. But, if we can give the option to use a medical interpreter with a script it may mean better follow-up rates at some sites. Rose, let us know if this is the conclusion from your discussions with Lisa Freund.

As for parent questionnaires - I think that an interpreter is perfectly fine. All the "standardized" questionnaires we have chosen come in Spanish (because we pretty much decided that was a non-starter if they didn't).

Jamie and Jane - I will send a follow-on email re: suggestions to the questions/check list that Jane drafted.

Thanks

Susan

> Thanks for working on this, Jane. We're finding that the Centers doing the Hypothermia 6-7 year do not have a Spanish-speaking examiner on hand to perform the WISC-IV (they'll need to find a Spanish-speaking examiner in the community and pay them to do the WISC-IV). I am not clear on which of these measures can be administered by an interpreter and which ones will need to be administered by a Spanish-speaking examiner so that information may be helpful to add to the table. We're lucky to have the experience of Hypo Ext Follow-up so that we can think through and plan for the language issue in advance.
>
> Thanks, Jamie
>
> -----Original Message-----
> From: Hammond, Jane
> Sent: Saturday, January 31, 2009 10:33 AM
> To: 'Susan Hintz'
> Cc: Newman, Jamie
> Subject: Support request to sites for info

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Here is my first attempt at this...see what you think. And here's my logic behind the grid. For assessments it is going to be important to know if they have the test kits because those are expensive. For the questionnaires I assumed that we would be buying those so the cost is not the issue and having access to them doesn't really matter even if they don't currently administer them.

Hmmmmm.....just thought of another question we might add. Should we ask if sites have a Spanish speaking individual who could a) administer some or all assessments or b) only administer questionnaires ? Not sure how to word that the most efficient way. To me "assessments" would refer to NEPSY or WISC and assumes some psych administration training. Questionnaires can be done by lots of people.

But - maybe you see the logic differently. Please weigh in. The goal is to make sure we only ask once (it at all possible) so I'm certainly open to making changes - this is just first draft.

Jane
P.S. - if we have a bunch of kids and parents who only speak Spanish, how are the docs/nurses dealing with this when kids come in for FU visits ?

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, January 30, 2009 5:24 PM
To: Hammond, Jane
Subject: battery grid as of 1/13/09

Here you go -

S
--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Melissa Leps; Nancy Miller
Subject: RE: New SUPPORT infant--2nd Adverse Event
Date: Friday, January 30, 2009 9:41:20 PM

I agree--it's the same (b) (6) ----pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/30/09 2:20 PM >>>
it s the same related event - just add this to the original AE

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Fri 1/30/2009 1:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Nancy Miller; Pablo Sanchez
Subject: Re: New SUPPORT infant--2nd Adverse Event

Rose,
They just finished up rounds on this infant. Regarding your question about the first tube possibly not draining--it was bubbling but Dr. Rosenfeld did feel it was not adequately working. When the 2nd chest tube was placed the infant responded very quickly--FiO2 decreased and blood pressure MAP quickly increased. Ultimately, they felt the air had reacumulated, and the 2nd chest tube resolved it.

So, would this be a second adverse event or an addition to the first event?
Kris??

Thanks

Missy

Missy Leps, RN
Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206.(b) (6)
fax: 214.648.2481

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/30/2009 8:34 AM >>>

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Thanks, was there a thought that the first tube was not draining air and that prompted a second tube?
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; Kristin Zaterka-Baxter ; Nancy Miller ; Pablo Sanchez
Sent: Fri Jan 30 09:09:02 2009
Subject: New SUPPORT infant--2nd Adverse Event

Kris,
The same infant I informed you about yesterday now has a 2nd chest tube--right side again, I am unsure if it's the same lobe. I have not been able to review the progress notes yet but will and then will let you know details.
This infant also may(b) (6) .

Just wanted to keep you up to date. I don't think this (b) (6) is study related either, but if I see something in the notes to make me think otherwise, I will let you know.

Thanks

Missy Leps, RN
Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
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From: Hamer, Faithe Angeline
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B; Wilson, Leslie Dawn; Dusick, Anna M.
Subject: SUPPORT query
Date: Friday, January 30, 2009 4:04:37 PM

Hi,
I am following up on the following conflicting data:

12 (b) (6) FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed

The NF05 has since been marked complete. Also, the NF10 was accidentally keyed as 1 for Q.A.2 – since the form was marked complete, I was unable to remove the 1 and save the form as incomplete. Therefore we have temporarily marked "6 – child seen, but incomplete visit" temporarily until the Bayley III is completed on the appt scheduled for (b) (6) I will at that time change the data back and key the NF11 and NF09A, as well.

Thanks so much!

Faithe Hamer
Research Assistant
fahamer@iupui.edu (email)
278-7364 (phone)
274-8963 (fax)
312(b) (6) (pager)

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: FW: New SUPPORT infant--2nd Adverse Event
Date: Friday, January 30, 2009 1:21:05 PM

I see this as one event– the MOP does not clarify. They should only complete one MedWatch with explanation of what transpired correct?.

Thanks,

Kris

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Friday, January 30, 2009 1:10 PM
To: Rosemary (NIH/NICHD) [E] Higgins; Zaterka-Baxter, Kristin; Nancy Miller; Pablo Sanchez
Subject: Re: New SUPPORT infant--2nd Adverse Event

Rose,
They just finished up rounds on this infant. Regarding your question about the first tube possibly not draining--it was bubbling but Dr. Rosenfeld did feel it was not adequately working. When the 2nd chest tube was placed the infant responded very quickly--FiO2 decreased and blood pressure MAP quickly increased. Ultimately, they felt the air had reacumulated, and the 2nd chest tube resolved it.

So, would this be a second adverse event or an addition to the first event?
Kris??

Thanks

Missy

Missy Leps, RN

Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/30/2009 8:34 AM >>>

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Rose
Rosemary D. Higgins, MD
Program Scientist

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From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; Kristin Zaterka-Baxter ; Nancy Miller ; Pablo Sanchez
Sent: Fri Jan 30 09:09:02 2009
Subject: New SUPPORT infant--2nd Adverse Event

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This infant also may(b) (6) . (b) (6) .

Just wanted to keep you up to date. I don't think this(b) (6) is study related either, but if I see something in the notes to make me think otherwise, I will let you know.

Thanks

Missy Leps, RN

Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
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From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Nancy Miller; Pablo Sanchez
Subject: Re: New SUPPORT infant--2nd Adverse Event
Date: Friday, January 30, 2009 9:47:10 AM

Rose,
I'll check with the resident and attending and let you know.

Thanks

Missy Leps, RN
Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206(b) (6)
fax: 214.648.2481

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/30/2009 8:34 AM >>>

Thanks, was there a thought that the first tube was not draining air and that prompted a second tube?
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Melissa Leps
To: Higgins, Rosemary (NIH/NICHD) [E]; Kristin Zaterka-Baxter ; Nancy Miller ; Pablo Sanchez
Sent: Fri Jan 30 09:09:02 2009
Subject: New SUPPORT infant--2nd Adverse Event

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Missy Leps, RN
Senior Research Nurse
Department of Pediatrics
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fax: 214.648.2481

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Adverse Event regarding new SUPPORT infant
Date: Thursday, January 29, 2009 4:24:31 PM

Just FYI below.

Thanks,

Kris

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Thursday, January 29, 2009 4:23 PM
To: Zaterka-Baxter, Kristin
Subject: RE: Adverse Event regarding new SUPPORT infant

Kris,
It's not likely.

Missy

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 1/29/2009 3:07 PM >>>

Hi Missy, do you know if this event was related to study in any way?

Appreciate it,

Kris

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Thursday, January 29, 2009 4:03 PM
To: Rosemary (NIH/NICHD) [E] Higgins; Zaterka-Baxter, Kristin; Nancy Miller; Pablo Sanchez
Subject: Adverse Event regarding new SUPPORT infant

Kris,
We had a new SUPPORT infant deliver on (b) (6). She was (b) (6) weeks and randomized to early intubation and surfactant. She received surfactant within the first hour of life and then a second dose at eight hours of life.
At 12-14 hours of life she developed (b) (6) and (b) (6).
Nancy is aware of this infant and you will be receiving the paperwork soon. She does not even have a network number yet.

Please let us know if there is anything else you need immediately.

Thanks

Missy Leps, RN

Senior Research Nurse
Department of Pediatrics
Division of Neonatal/Perinatal Medicine

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From: Danny Benjamin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial
Date: Wednesday, January 28, 2009 1:14:09 PM

---

thanks rose. i am happy to send full protocol if that is helpful. i didn't even think to send it forward because it is a pk trial

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University Pediatrics
Chief, Division of Quantitative Sciences
Director, DCRI Clinical Research Fellowship Program

2400 Pratt St.
Duke Clinical Research Institute Durham NC 27715
Ph: 919-668-8295; Fax: 919-681-9457

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

01/28/2009 12:00 PM

To "Michael Cotten" <cotte010@mc.duke.edu>, "Rich, Wade" <wrich@ucsd.edu>
cc "Benjamin, Danny" <BENJA005@dcri.duke.edu>
Subject RE: Support baby and mirapenim trial

I just sent out a vote to the concurrent research committee

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, January 28, 2009 11:45 AM
To: Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Benjamin, Danny
Subject: RE: Support baby and mirapenim trial

HI all,,,

I'll check w/ Danny about full protocol as he's study PI, here's the synopsis from the study abstract included in the protocol document.

it's a pK trial enrolling 200 kids to get meropenem at different doses/schedules depending on gestational and postnatal chronologic age. endpoints are primarily pK and safety.

(See attached file: meropenem summary pdf copy.doc)

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Rich, Wade"
<wrich@ucsd.edu>

To

01/28/2009 09:58 "Higgins, Rosemary (NIH/NICHD) [E]"

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AM <higginsr@mail.nih.gov>

cc <cotte010@mc.duke.edu>

Subject RE: Support baby and mirapenim trial

I can send you the protocol with Mike's permission.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 28, 2009 6:54 AM
To: Das, Abhik; Finer, Neil; Zaterka-Baxter, Kristin
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

Can we get a summary of the study - I was not sure whether this was a pK study or trial based on Kris's email. The vast majority of the time, concurrent studies are allowed.

Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, January 28, 2009 9:51 AM
To: Finer, Neil; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

I tend to agree with Neil, but am not sure whether we need a formal ruling
from the concurrent studies subcommittee.

Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 27, 2009 12:13 PM
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Das, Abhik
Subject: RE: Support baby and mirapenim trial
Hello Everyone
We have not discussed this. The meropenum study is for pharmacokinetics and
it has usually been decided that the infant will get meropenum apart from
the research study. There is no placebo arm for this study. The only potential conflict could be blood draws - SUPPORT doesn't require any. I do
not believe that there is any conflict with SUPPORT.
The answer to your question from my perspective is YES.

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, January 27, 2009 6:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Finer, Neil; Das, Abhik
Subject: Support baby and mirapenim trial

Hi,
Can a Support trial baby (on day 9 of the trial; DOB(b) (6) also be enrolled in the mirapenim trial for NEC?
Thanks,
Kris

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Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
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Kris Zaterka-Baxter
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RTP, NC 27709 USA

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From: Michael Cotten
To: Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Benjamin, Danny
Subject: RE: Support baby and mirapenim trial
Date: Wednesday, January 28, 2009 11:45:35 AM
Attachments: meropenem summary pdf copy.doc

HI all,,,

I'll check w/ Danny about full protocol as he's study PI, here's the synopsis from the study abstract included in the protocol document.

it's a pK trial enrolling 200 kids to get meropenem at different doses/schedules depending on gestational and postnatal chronologic age. endpoints are primarily pK and safety.

(See attached file: meropenem summary pdf copy.doc)

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Rich, Wade"
<wrich@ucsd.edu>
01/28/2009 09:58 AM

To
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
cc
<cotte010@mc.duke.edu>
Subject
RE: Support baby and mirapenim trial

I can send you the protocol with Mike's permission.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

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Can we get a summary of the study – I was not sure whether this was a pK study or trial based on Kris's email. The vast majority of the time, concurrent studies are allowed.

Rose

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Sent: Wednesday, January 28, 2009 9:51 AM
To: Finer, Neil; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

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Thanks

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Sent: Tuesday, January 27, 2009 12:13 PM
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The answer to your question from my perspective is YES.

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, January 27, 2009 6:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Finer, Neil; Das, Abhik
Subject: Support baby and mirapenim trial

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Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
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3040 Cornwallis Road
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PROTOCOL SYNOPSIS

Protocol Title	Multiple Dose Pharmacokinetic Study of Meropenem in Young Infants (<91 days) with Suspected or Complicated Intra-abdominal Infections
Sponsor:	NICHD
Product	Meropenem
Objectives:	a. To characterize meropenem single-dose and multiple-dose PK in subjects with suspected or complicated intra-abdominal infections. b. To characterize the safety profile of meropenem in the treatment of suspected or complicated intra-abdominal infections. c. To assess collected efficacy data for meropenem for the treatment of suspected or complicated intra-abdominal infections.
Study Design:	Multi-center, prospective, pharmacokinetic and safety study of meropenem for the treatment of suspected or complicated intra-abdominal infections
Study Population:	Premature and term young infants (<91 days) who have a suspected or early complicated intra-abdominal infection. These subjects must be subdivided into the following four groups: Group 1: GA at birth below 32 weeks - PNA < 2 weeks; Group 2: GA at birth below 32 weeks - PNA ≥ 2 weeks and < 91 days; Group 3: GA at birth 32 weeks or older - PNA < 2 weeks; Group 4: GA at birth 32 weeks or older - PNA ≥ 2 weeks and < 91 days.
Number of Infants:	Approximately 200 infants that complete the study
Number of Sites:	Approximately 25
Treatment:	Meropenem Aminoglycoside should be administered in conjunction with meropenem. Additional antimicrobial coverage may be added per standard of care.
Treatment Duration	At least 3 days; otherwise, per local standard of care (maximum 21 days)
PK/PD:	Minimal sampling and population PK will be employed
Safety:	The protocol will rely on three mechanisms for safety: 1) The DSMB 2) Adverse event and SAE reporting mechanisms 3) The active, daily, real time oversight of the MPODS Clinical Safety Committee All serious adverse events (SAEs) will be closely monitored throughout the course of the study. Seizures will be intensely monitored and clinical laboratories of renal, and hepatic toxicity monitored weekly as available per local standard of care. Safety assessments will include seizure documentation (including correlation of serum meropenem level and seizures), physical examination, clinical laboratory values, LFTs, renal function and nosocomial infections (tracked by pathogen).
Statistical Consideration:	The sample size is designed to assess single and multiple dose PK of meropenem in young infants. All infants who receive meropenem will be analyzed. These infants will comprise the population for the safety analysis, and if any PK samples are obtained, their blood will be evaluated in the PK analysis. Those infants who have an efficacy measurement at Day 28 will also be evaluated for clinical (efficacy) response. Key safety endpoints that will be evaluated in the final analysis: include death, seizures, strictures, perforation, wound dehiscence, short gut, development of extended beta lactamase infection, development of candidiasis, and antimicrobial therapy failure. The proportion of infants affected and 95% CI for each key safety endpoint will be reported. The following PK parameters will be estimated: a) Plasma clearance b) Volume of distribution c) Cmax, Tmax, AUC_{0-T}, (at steady state), Ke and $t_{1/2}$ $AUC_{0-\infty}$ (estimated from the 1st dose)
Inclusion Criteria	a. Written permission from parent or legal guardian b. Age younger than 91 days

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	c. Likely to survive beyond the first 48 hours after enrollment d. Sufficient intravascular access (either peripheral or central) to receive study drug AND ONE OF THE FOLLOWING e. 1) Physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection. These include peritonitis, NEC Grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous perforation, meconium ileus with perforation, bowel obstruction with perforation, as evidenced by free peritoneal air on abdominal radiograph, intestinal pneumotosis or portal venous gas on abdominal radiographic examination. OR 2) Possible NEC OR 3) Otherwise receiving meropenem per local standard of care
Exclusion Criteria	a. Renal dysfunction evidenced by urine output <0.5 mL/hr/kg over the prior 24 hours b. Serum creatinine >1.7 mg/dL c. History of clinical seizures or EEG confirmed seizures d. Concomitant treatment with another carbapenem (ertapenem or imipenem) at the time of informed consent e. Any condition which would make the subject or the caregiver, in the opinion of the investigator, unsuitable for the study

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Finer, Neil
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial
Date: Wednesday, January 28, 2009 10:05:48 AM

I have asked Leslie Wilson for a summary and will forward to all when I get it.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 28, 2009 9:54 AM
To: Das, Abhik; Finer, Neil; Zaterka-Baxter, Kristin
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

Can we get a summary of the study – I was not sure whether this was a pK study or trial based on Kris's email. The vast majority of the time, concurrent studies are allowed.

Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, January 28, 2009 9:51 AM
To: Finer, Neil; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

I tend to agree with Neil, but am not sure whether we need a formal ruling from the concurrent studies subcommittee.

Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 27, 2009 12:13 PM
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Das, Abhik
Subject: RE: Support baby and mirapenim trial

Hello Everyone
We have not discussed this. The meropenum study is for pharmacokinetics and it has usually been decided that the infant will get meropenum apart from the research study. There is no placebo arm for this study. The only potential conflict could be blood draws – SUPPORT doesn't require any. I do not believe that there is any conflict with SUPPORT.
The answer to your question from my perspective is YES.

Neil

Neil N. Finer, M.D.

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Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, January 27, 2009 6:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Finer, Neil; Das, Abhik
Subject: Support baby and mirapenim trial

Hi,
Can a Support trial baby (on day 9 of the trial; DOB (b) (6) also be enrolled in the mirapenim trial for NEC?
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
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Kris Zaterka-Baxter
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RTP, NC 27709 USA

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support baby and mirapenim trial
Date: Wednesday, January 28, 2009 10:00:15 AM

The short answer is it is a multidose PK/Safety study.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 28, 2009 6:54 AM
To: Das, Abhik; Finer, Neil; Zaterka-Baxter, Kristin
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

Can we get a summary of the study – I was not sure whether this was a pK study or trial based on Kris's email. The vast majority of the time, concurrent studies are allowed.

Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, January 28, 2009 9:51 AM
To: Finer, Neil; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade
Subject: RE: Support baby and mirapenim trial

I tend to agree with Neil, but am not sure whether we need a formal ruling from the concurrent studies subcommittee.

Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 27, 2009 12:13 PM
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Das, Abhik
Subject: RE: Support baby and mirapenim trial

Hello Everyone
We have not discussed this. The meropenum study is for pharmacokinetics and it has usually been decided that the infant will get meropenum apart from the research study. There is no placebo arm for this study. The only potential conflict could be blood draws – SUPPORT doesn't require any. I do not believe that there is any conflict with SUPPORT.
The answer to your question from my perspective is YES.

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine

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402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, January 27, 2009 6:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Rich, Wade; Finer, Neil; Das, Abhik
Subject: Support baby and mirapenim trial

Hi,
Can a Support trial baby (on day 9 of the trial; DOB (b) (6) also be enrolled in the mirapenim trial for NEC?
Thanks,
Kris

Kris Zaterka-Baxter
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RTP, NC 27709 USA

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Tuesday, January 27, 2009 5:10:41 PM

As of data transmitted last week, we do not have an NF10 or NF12 for infant (b) (6) (follow up number (b) (6) Both should be filled out if the infant was lost to follow up.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 27, 2009 4:52 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: Fw: SUPPORT

Can you help with this, or should I ask Jenny?
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Karen Osborne RN
Sent: Tue Jan 27 16:46:30 2009
Subject: FW: SUPPORT
Hi Rose!

Karen is (b) (6) , so I asked our data entry coordinator Nichol to look into your query. I hope the info below is helpful. If you require further input prior to Karen's return, please let me know.

Roger

From: Nichol Nunn
Sent: Tue 1/27/2009 7:38 AM
To: Roger Faix
Cc: Karen Osborne RN; Bradley Yoder
Subject: RE: SUPPORT

Is Rose referring to the SF05 and SF09a which are the follow up forms for the SUPPORT program? We are now just using the GDB follow-up forms for all follow up. (b) (6) have not come in for their 18 month follow-up yet (b) (6) was lost to follow-up. NF00 and NF01 forms have been completed for (b) (6) and Shawna should be working on setting up an appointment. All of the appropriate paperwork for (b) (6) LTF status has been completed.

Nichol Nunn

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Data Entry Coordinator
Neonatal Research Network
University of Utah
Dept of Pediatrics, Division of Neonatology
PO Box 581289
Salt Lake City, UT 84158
Phone # (801) 213-3296

From: Roger Faix
Sent: Monday, January 26, 2009 11:40 AM
To: Nichol Nunn
Cc: Karen Osborne RN; Bradley Yoder
Subject: FW: SUPPORT

Hi Nichol!

In Karen's absence and upon your return, do you have an idea why these are missing (lost to follow-up; scheduled but not seen yet; not entered; etc.)?

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 1/23/2009 1:34 PM
To: Roger Faix; Bradley Yoder; Karen Osborne RN; abodnar@utah.gov
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing some SUPPORT primary outcomes. Please let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	FU_message
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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From:	Zaterka-Baxter, Kristin
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	cotte010@mc.duke.edu; wrich@ucsd.edu; nfiner@ucsd.edu; Das, Abhik; Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]
Subject:	RE: Support baby and mirapenim trial
Date:	Tuesday, January 27, 2009 10:54:00 AM

We do not seem to have a record of the meropenem trial being reviewed by the concurrent research subcommittee. I have asked Indiana about their IRB reg's.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 27, 2009 10:04 AM
To: Zaterka-Baxter, Kristin
Cc: cotte010@mc.duke.edu; wrich@ucsd.edu; nfiner@ucsd.edu; Das, Abhik
Subject: Re: Support baby and mirapenim trial

I do not recall that the concurrent research subcommittee has evaluated the meropenem study for conflict. Has this been done? I am not in the office today to check to see if this had been reviewed - if it was reviewed, we send an email to the investigator. Also, has the local irb weighed in on dual inclusion in the two trials?

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten ; Rich, Wade ; nfiner@ucsd.edu ; Das, Abhik
Sent: Tue Jan 27 09:49:54 2009
Subject: Support baby and mirapenim trial
Hi,
Can a Support trial baby (on day 9 of the trial; DOB (b) (6) also be enrolled in the mirapenim trial for NEC?
Thanks,
Kris

Kris Zaterka-Baxter
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RTP, NC 27709 USA

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From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, January 27, 2009 9:14:07 AM

Thanks Rose,
It was done and will be entered today if it hasn't already been entered.
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper (b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 23, 2009 3:30 PM
To: Frantz, Ivan; Mackinnon, Brenda
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing some SUPPORT primary outcomes. Please let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	BPD_message
23	(b) (6)	PHY01 is expected based on NG07 but has not been entered

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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higginsr@mail.nih.gov

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From: CATHY A. GRISBY
To: Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org
Cc: Gantz, Marie; Das, Abhik; Jeanette O. Auman
Subject: Re: SUPPORT
Date: Monday, January 26, 2009 2:35:01 PM

Hi,

I have been emailing Jenny about the coding for these babies and I hope we have these addressed.

Here are the situations for these babies.

(b) (6) did not have a second exam in Zone III as required for endpoint. The ophthomalogist wrote for 1 year follow up after this exam. This baby has been seen for the follow up visit and has vision.

(b) (6) has multiple health issues as well as a noncompliant mother. Mom had the eye exams very low on the priority list of appointments she did actually bring him to.

Thanks,

Cathy

---- Original message ----

Date: Fri, 23 Jan 2009 15:13:16 -0500
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject: SUPPORT
To: <kurt.schibler@cchmc.org>, <grisbyca@email.uc.edu>
Cc: "Gantz, Marie" <mgantz@rti.org>, "Das, Abhik" <adas@rti.org>

Hi,

We are missing some SUPPORT primary outcomes. Please let us know how you are doing.

Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
11	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
11	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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and Human Development

National Institutesof Health

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From: Zaterka-Baxter, Kristin
To: Johnson, Mary; rbara@med.wayne.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support AE #7805-2
Date: Monday, January 26, 2009 12:31:46 PM

Thanks Mary, I received your fax for this AE; can you please confirm the event was not thought to be related to study?

Appreciate it,
Kris

Kris Zaterka-Baxter
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RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
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From: Vohr, Betty
To: Ira Adams-Chapman; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Saturday, January 24, 2009 5:49:50 AM

Ira and Rose,
Ira, You are correct. We should have a call for input. Rose, can we query all follow-up PIs regarding the Bayley III ?
Does your site administer only the cognitive and language composites at 18m ?
Does your site ever administer the total Bayley III ?
How long does it take ?
For this call we should also have the gold standards on the call.
The issue of high scores is another issue.
I was wondering if some of the sites that are doing the motor component could share those results.
We are doing the total Bayley III at 7 months and I know there are sites admininistering all at 18 months.

I am on my way to (b) (6) and will be out all day.
Hope we can discuss on Monday.
BV

From: Ira Adams-Chapman [Ira_Adams-Chapman@oz.ped.emory.edu]
Sent: Friday, January 23, 2009 9:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vohr, Betty
Subject: Re: SUPPORT

Hi Rose and Betty,
Is there a plan for the folllowup PI's to have a conference call to discuss the concerns about the Bayley III data? I think that it would definitely be helpful particularly since we will not meet as a group for several months. Just checking -

Ira Adams-Chapman, MD
Director, Developmental Progress Clinic
Assistant Professor of Pediatrics
Emory University School of Medicine
Department of Pediatrics/Division of Neonatology

404-778-1450 (O)
ira_adams-chapman@oz.ped.emory.edu

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Subject: RE: Potential PAS Abstract
Date: Friday, January 23, 2009 3:57:28 PM

Hi Dale
I think this is a good idea. Once we have the final eye data, you could begin to look. I would like t get the primary papers done first – so I think 2010 is good – As far as I am concerned you can take the lead for this.
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 23, 2009 10:44 AM
To: dale_phelps@urmc.rochester.edu; Finer, Neil
Subject: Re: Potential PAS Abstract

Great question -
Primary outcome analyses would need to be done first. Also, did you and Kathleen Kennedy bring this up previously?

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Phelps, Dale
To: nfiner@ucsd.edu ; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Jan 23 13:40:26 2009
Subject: Potential PAS Abstract
Hi Neil and Rose,

I have an idea, but I have been waiting for the SUPPORT data. Someone else may have already put in a request to do it. This is fine, I just want to be sure it is done, and I would be happy to help if there is already a leader.

The SUPPORT data will give us for the first time a solid dataset on what happens to ROP before vs after transfer or discharge. It will let us estimate the proportion of infants in major centers that really do have surprises after "status". Up to this point, neonatologists have almost always published 'what happened while they were in our hospital". This will let us estimate the error introduced by incomplete early follow up.

Neil, if someone is already planning this, just tell me to back off. (I have plenty to do with inositol).

Also, maybe 2010 may be too early since you'll be dealing with the primary outcomes and will not want to muck with this right away.

Your advice?

Dale

Dale L. Phelps, MD
Professor of Pediatrics
274 Corte Madera Road

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From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; "nancy newman"
Cc: "Gantz, Marie"; "Das, Abhik"
Subject: RE: SUPPORT
Date: Friday, January 23, 2009 3:11:32 PM

This mother has missed 3 appts. and has been reported to the county. Still tracking.
Bonnie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 23, 2009 3:07 PM
To: mcw3@cwru.edu; nancy newman; Bonnie Siner
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing some SUPPORT primary outcomes. Please let us know how you are doing. This is amazing considering the outstanding recruitment at Case!!!
Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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higginsr@mail.nih.gov

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Friday, January 23, 2009 2:20:32 PM
Attachments: Infants with missing outcomes 01-23-09.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
11		The patient is within their Fol-up window and final ROP status has not been reported.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		The patient is within their Fol-up window and final ROP status has not been reported.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
19		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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From: Auman, Jeanette O.
To: Kristi Watterberg
Cc: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Subject: RE: enrollment report for SUPPORT, UNM
Date: Wednesday, January 21, 2009 4:43:09 PM

I'm reviewing this now and will update you as soon as I find the issue.

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Wednesday, January 21, 2009 1:58 PM
To: Auman, Jeanette O.
Cc: Rosemary (NIH/NICHD) Higgins; Zaterka-Baxter, Kristin
Subject: enrollment report for SUPPORT, UNM

Hi. Our SUPPORT report must be wrong. We have enrolled a total of 17 babies as of December 2008, but this report gives us credit for 36 in the last year (not that that wouldn't be nice!!)

Can you help? thanks, Kristi

Kristi Watterberg, M.D.
Professor and Chief, Division of Neonatology

Vice Chair, Dept. of Pediatrics
MSC10 5590
1 University of New Mexico
Albuquerque, New Mexico 87131

Office Phone: (505) 272-0180
FAX: (505) 272-1539
E-mail: kwatterberg@salud.unm.edu

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; ifrantz@tuftsmedicalcenter.org
Cc: bmackinnon@tuftsmedicalcenter.org; poo@rti.org; mgantz@rti.org
Subject: RE: Support randomization question
Date: Tuesday, January 20, 2009 2:34:10 PM

I do not have a problem with this potential randomization
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 20, 2009 7:44 AM
To: adas@rti.org; ifrantz@tuftsmedicalcenter.org; Finer, Neil
Cc: bmackinnon@tuftsmedicalcenter.org; poo@rti.org; mgantz@rti.org
Subject: Re: Support randomization question

One more question - do yoave four of each color of oximeter available? If you need more, let us know and we will find them for you

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Das, Abhik
To: Frantz, Ivan ; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Mackinnon, Brenda ; Poole, W. Kenneth ; Gantz, Marie
Sent: Tue Jan 20 10:38:10 2009
Subject: RE: Support randomization question
I dont see any problem; do you? The oximeters will remain blinded and the other arm of the trial is not blinded anyway.

Thanks

Abhik

From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Tuesday, January 20, 2009 10:35 AM
To: higginsr@mail.nih.gov; Finer, Neil; Das, Abhik
Cc: Mackinnon, Brenda
Subject: Support randomization question

I am in discussion with the parents of a set of quads about support enrollment. There is a possibility of "interval delivery" of quad A, who has ruptured membranes. Should this occur we will know some time prior to delivery which group the others will be randomized to. While the interval will likely be short, it could be prolonged to days or more. Any issues with this?

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Ivan D. Frantz, III, M.D.
Professor of Pediatrics
Tufts University School of Medicine

Tufts Medical Center Box 44
800 Washington St.
Boston, MA 02111

617 636 5322

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From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Frantz, Ivan; nfiner@ucsd.edu
Cc: poo@rti.org; mgantz@rti.org
Subject: RE: Support randomization question
Date: Tuesday, January 20, 2009 10:57:15 AM

Hi,
No thank you I got them mobilized last Friday for the weekend incase the consented and delivered as she admitted at the end of the work day on Friday
Brenda

Brenda MacKinnon, RNC NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box # 44
Boston, Ma 02111

Beeper #(b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 20, 2009 10:44 AM
To: adas@rti.org; Frantz, Ivan; nfiner@ucsd.edu
Cc: Mackinnon, Brenda; poo@rti.org; mgantz@rti.org
Subject: Re: Support randomization question

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Rose
Rosemary D. Higgins, MD
Program Scientist

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Cc: Mackinnon, Brenda ; Poole, W. Kenneth ; Gantz, Marie
Sent: Tue Jan 20 10:38:10 2009
Subject: RE: Support randomization question
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Sent: Tuesday, January 20, 2009 10:35 AM
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Cc: Mackinnon, Brenda
Subject: Support randomization question

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Boston, MA 02111

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From: Das, Abhik
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support randomization question
Date: Tuesday, January 20, 2009 10:54:37 AM

You are way ahead of us!

Thanks

Abhik

From: Zaterka-Baxter, Kristin
Sent: Tuesday, January 20, 2009 10:49 AM
To: Das, Abhik
Subject: RE: Support randomization question

I sent brenda what she needed – delivered on Sat at her home.
thanks

From: Das, Abhik
Sent: Tuesday, January 20, 2009 10:46 AM
To: Zaterka-Baxter, Kristin
Subject: FW: Support randomization question

FYI

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 20, 2009 10:44 AM
To: Das, Abhik; ifrantz@tuftsmedicalcenter.org; nfiner@ucsd.edu
Cc: bmackinnon@tuftsmedicalcenter.org; Poole, W. Kenneth; Gantz, Marie
Subject: Re: Support randomization question

One more question - do yoave four of each color of oximeter available? If you need more, let us know and we will find them for you

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Das, Abhik
To: Frantz, Ivan ; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Mackinnon, Brenda ; Poole, W. Kenneth ; Gantz, Marie
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Abhik

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From: Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]
Sent: Tuesday, January 20, 2009 10:35 AM
To: higginsr@mail.nih.gov; Finer, Neil; Das, Abhik
Cc: Mackinnon, Brenda
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Ivan D. Frantz, III, M.D.
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From: Newman, Jamie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Object Permanence Ancillary - approved by SUPPORT subcommittee
Date: Monday, January 19, 2009 5:19:36 PM

Rose,

We should be able to add the Object Permanence Ancillary form to the Data Entry system fairly quickly. Has the SC approved this addition? I realize the SUPPORT subcommittee has approved it. Once we receive word that the SC has approved this, we will add it to the data entry system. I have not received any replies from my Jan 12 email below.

Thanks, Jamie

From: Newman, Jamie
Sent: Monday, January 12, 2009 12:03 PM
To: '[SCRN] Stoll, Barbara (barbara_stoll@oz.ped.emory.edu)'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bell, Edward'; 'bpoindex@iupui.edu'; 'Das, Abhik (adas@rti.org)'; 'goldb008@mc.duke.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'ifrantz@tuftsmedicalcenter.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'mca113@northwestern.edu'; 'mcw3@cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'richard.ehrenkranz@yale.edu'; 'Roger.Faix@hsc.utah.edu'; 'sshankar@med.wayne.edu'; 'vanmeurs@leland.stanford.edu'; 'Wally Carlo, M.D.'; (b) (6) '; 'Roy.Heyne@utsouthwestern.edu'; 'ira_adams-chapman@oz.ped.emory.edu'; 'Kimberly.Yolton@cchmc.org'; 'steichjj@email.uc.edu'; 'adusick@iupui.edu'; 'bvohr@wihri.org'; 'srhintz@stanford.edu'; 'MPeralta@PEDS.UAB.EDU'; 'Patricia.W.Evans@uth.tmc.edu'; 'golds005@mc.duke.edu'; 'emcgowan@tuftsmedicalcenter.org'; 'michael-acarregui@uiowa.edu'; 'abodnar@utah.gov'; 'jafuller@salud.unm.edu'
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Auman, Jeanette O.; Huitema, Carolyn Petrie; Gantz, Marie; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: Object Permanence Ancillary - approved by SUPPORT subcommittee

Dear Steering Committee and Follow-up PIs,

The SUPPORT Subcommittee has approved the Object Permanence Ancillary to the neuroimaging cohort, which involves one new form. The protocol and short data collection form are attached.

Please note that the protocol is titled "ANCILLARY STUDY TO SUPPORT FOLLOW UP: Evaluation of early working memory in extremely preterm infants" though it is being referred to it as the "Object Permanence Ancillary."

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
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Jamie Newman
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RTP, NC 27709 USA

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From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kris Zaterka-Baxter
Subject: Re: support patient death
Date: Tuesday, January 13, 2009 9:25:22 AM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

>Was this study related? Can you fax me the medwatch?
>Thanks
>Rose
>
>-----Original Message-----
>From: Monica Konstantino [mailto:monica.konstantino@yale.edu]
>Sent: Tuesday, January 13, 2009 8:59 AM
>To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
>Subject: support patient death
>
>Hi, I wanted to let you know that one of our support patients, network #
>
(b) (6) l died on (b) (6) The baby was [redacted] days old born at (b) (6) weeks (b) (6) [redacted] and the baby was removed from the
>vent. I am faxing a Med Watch form to Kris. thanks,
>Monica
>
>
>

I just faxed you the medwatch as well. His death does not appear to be study related, the baby had been randomized to early CPAP but had to be intubated in the DR with (b) (6) [redacted]. The Mom decided to withdraw support after many meetings with our staff. Let me know if you need any more info.
Monica

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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B
Subject: RE: SUPPORT
Date: Monday, January 12, 2009 3:34:57 PM

Hi.

(b) (6)-Pt is deceased and NF10 and NF12 are being completed.
(b) (6)-NF5 is entered, NF9 appt is to be scheduled and NF10 will be corrected to reflect that pt not completed visit.
(b) (6)-Pt is completed.

Kind Regards-leslie

lie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 19, 2008 3:38 PM
To: Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. The trial is coming to an end and we would like to have missing data entered as quickly as possible. Please let us know how you are doing. Thanks for all the hard work and effort!!
Rose

CENTER	NETWORK	BPD_message
12	(b) (6)	PHY01 is expected based on NG07 but has not been entered
CENTER	NETWORK	FU_message
12	(b) (6)	There is an NF12 reflecting that the infant died, but please fill out an NF10 as well
12	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: support secondary concept
Date: Monday, January 12, 2009 2:55:58 PM

Hi Rose....got this per Neil....I don't want to oversell network potential to collect dna for support kids,,,,,but I think (and I'm probably wrong) that since the proposal originated in the network I should be able to mention where its at the network

Mc

----- Original Message -----
From: "Finer, Neil" [nfiner@ucsd.edu]
Sent: 01/12/2009 08:58 AM PST
To: Michael Cotten
Subject: RE: support secondary concept

Hi Mike
This looks very complete and very good. I would totally support this.
Be well
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Monday, January 12, 2009 8:30 AM
To: Finer, Neil
Subject: support secondary concept

Hi Neil...

you probably know (or maybe not) that I submitted a concept protocol
that
is really a secondary to SUPPORT entitled :Do Genetic Variations
Influence
ROP risk at High vs. Low Oxygen Saturation Target Range? The protocol
would
ask for DNA samples (oral swabs) from infants enrolled in SUPPORT who
are
returning either for 18 - 22 month followup or the later followup
involved
w/ neuroimaging. We would target looks at pathways to identify groups of

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candidate genes from VEGF, HIF1alpha, and angiogenesis pathways....and use
tagSNP's to try to ID regions of genes in those pathways that are associated w/ ROP risk. The concept was approved 17 - 1, so we're working
on a full protocol to come back quickly for protocol committee review.....

I apologize for not talking much about this prior to submission of the concept...but I"m never sure about asking for anyone's time before it looks
like it's going anywhere. I don't think the DNA will affect participation
in the main trial the way we are approahing only on followup. I think there's a unique opportunity because of the detailed characterization of rop phenotype and the oxygen exposure data. Also,,,Lex Doyle mentioned that
he would be interested in sending a secondary to BOOST II committee leadership to collect DNA, independent of the Network's decision.

So...for this email, I'm sending the power point we presented last week....as the protocol develops if I may I"ll send it on.

thanks

mc

(See attached file: support genotype 1.9.09.ppt)

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

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From:	Newman, Jamie
To:	barbara_stoll@oz.ped.emory.edu; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; adas@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; (b) (6) .Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; Kimberly.Yolton@cchmc.org; steichji@email.uc.edu; adusick@iupui.edu; bvohr@wihri.org; srhintz@stanford.edu; MPeralta@PEDS.UAB.EDU; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; emcgowan@tuftsmedicalcenter.org; michael-acarregui@uiowa.edu; abodnar@utah.gov; jafuller@salud.unm.edu
Cc:	Zaterka-Baxter, Kristin; Cunningham, Meg; Auman, Jeanette O.; Huitema, Carolyn Petrie; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]
Subject:	Object Permanence Ancillary - approved by SUPPORT subcommittee
Date:	Monday, January 12, 2009 12:03:29 PM
Attachments:	Object permanence ancillary proposal revised 10-2008.doc Obj_Perm_Ancillary_SUPPORT_MRI09A.doc

---

Dear Steering Committee and Follow-up PIs,

The SUPPORT Subcommittee has approved the Object Permanence Ancillary to the neuroimaging cohort, which involves one new form. The protocol and short data collection form are attached.

Please note that the protocol is titled "ANCILLARY STUDY TO SUPPORT FOLLOW UP: Evaluation of early working memory in extremely preterm infants" though it is being referred to it as the "Object Permanence Ancillary."

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
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newman@rti.org

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REVISED PROPOSAL FOR ANCILLARY STUDY TO SUPPORT FOLLOW UP:

Evaluation of early working memory in extremely preterm infants (10-29-08)

Protocol development group:

Jean Lowe Ph.D., Janell Fuller, MD, Kristi Watterberg, MD (UNM)

Susan Hintz, MD (Stanford)

Abstract: We propose to study early working memory in extremely preterm infants enrolled in the NICHD SUPPORT trial by recording and analyzing responses to 3 specific items from the Bayley Scales of Infant Development-III (Bayley-III) which measure object permanence (items 40, 45 and 50), and evaluating the relationship of "mastery of object permanence" to (1) performance on the Bayley-III at 18 – 22 months, (2) to MRI findings at term gestation, and (3) to performance on tests of executive function at 6 – 7 years of age.

Hypotheses:

1. Randomization to higher vs. lower oxygen saturation target ranges in the SUPPORT study will not affect the attainment of object permanence as assessed by the Bayley-III test of Cognition and Language at 18-22 months.
2. Among all children born extremely preterm (<28 0/7 weeks gestation), those who achieve object permanence mastery will do significantly better on the Bayley-III test of Cognition and Language at 18-22 months than those who do not.

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3. Among all infants born extremely preterm, object permanence mastery at 18 months will not be affected by SES or ethnic grouping, in contrast to Bayley III Cognitive and Language scores.
4. Among those children born extremely preterm who had MRI scans at term, those who achieve object permanence mastery will have significantly fewer abnormal findings on the MRI performed at term as part of the SUPPORT trial.
5. Among those children born extremely preterm who had MRI scans at term, those who achieve object permanence mastery will perform significantly better on tests of executive function at 6 and 7 years.

Background and significance:

Executive function is an umbrella term that encompasses three main areas: working memory, inhibition, and cognitive flexibility (Davidson 2005). Recently we have seen more studies that look at working memory as a measure of executive functioning in school age outcome studies (Anderson 2004, Curtis 2002, Luciana 1999) with significant differences found between executive functioning in those children born preterm in comparison to children born at term. Studies have shown executive function deficits in children school-aged and older who were born prematurely (Anderson 2004), which persist even after taking IQ differences into account (Bayless 2007).

In one of the few studies of executive function with young children born preterm Woodward et al (2005) found that 2 year olds born preterm had difficulty encoding new information in working memory compared to term infants, and that on MRI children born preterm had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parieto-occipital and premotor areas).

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Studying these vulnerable populations at younger ages could result in executive function interventions that could be clinically useful. New measures have recently been developed which allow researchers to tap into the foundations of executive function in very young children, particularly their working memory, impulse control, and rule use (Carlson 2005). Although these new measures for preschool children have been employed with typically developing populations (Carlson 2005), there are currently very few studies investigating executive function in preschool children born prematurely. The few studies that have been conducted found that preschoolers born VLBW without major neurological deficits may have specific difficulty in sustained attention, visuospatial processing, and spatial working memory when compared with full term children matched for chronological age and IQ (Vicari 2004).

A recent randomized trial of early hydrocortisone treatment (Watterberg 2007) found that fewer hydrocortisone-treated patients had a Bayley-II MDI of <70 and that more of the hydrocortisone-treated children showed evidence of awareness of object permanence on the Bayley-II. Further investigation indicated that MDI scores were significantly higher in the white ethnic group while object permanence mastery was relatively similar across all ethnic groups (Blacks, Hispanics, Asians, whites) (Lowe, in press).

Our finding that object permanence mastery is not affected by either ethnic group or income could significantly improve our ability to identify children who are at-risk for later developmental sequelae, as the Bayley MDI – which is affected by those factors – is a poor predictor of later cognitive function (Hack 2005). Object permanence items as a measure of early working memory (Diamond 1997) have been related to the development

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of prefrontal cortical function (Woodward 2005) and the earliest measure of reasoning skills in toddlers. This is relevant to intervention techniques that can be developed to specifically work on tasks that could enhance these skills. In conjunction with the Bayley Scales cognitive score, use of a measure of object permanence may also improve our detection of ongoing problems with executive function at 18-22 months, which is highly related to later learning difficulties. We therefore speculate that measurement of object permanence at 18 – 22 months will be a useful predictor of executive function at 6 – 7 years of age, and therefore may improve our ability to provide early intervention services to this population.

Methods:

We propose to prospectively record pass/fail for items 40, 45 and 50 from the Bayley-III Cognitive Scale in infants enrolled in the SUPPORT trial when they are evaluated at 18 – 22 months adjusted age. These object permanence items sequentially increase in difficulty. First, the child is asked to find a toy hidden under one of two cups (item 40). Second, the cups are reversed after the toy is hidden (item 45). Third, double visual displacement is used: the toy is hidden under one cup, removed and hidden a second time under the second cup (item 50). The number of object permanence items correctly completed is calculated for each child and used as an ordinal measure.

Because the SUPPORT study interventions are randomized, the analysis of the relationship of attainment of object permanence to the measures outlined in the hypotheses above should not be confounded by those interventions. We will test the null hypothesis that randomization to high vs. low saturation targets on "mastery of object

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permanence" (**hypothesis #1).** We will then analyze (1) the relationship of 'mastery of object permanence', defined as achievement of two of these items, to performance on the Bayley-III Cognitive scale (**hypothesis #2)**; (2) the effect of SES and ethnic grouping on performance in both the cognitive scale and object permanence achievement **(hypothesis #3)**; (3) the relationship of mastery of object permanence to MRI findings at term gestation in those infants enrolled in the Neuroimaging secondary of the SUPPORT trial, specifically the number and/or size of lesions in the prefrontal, parieto-occipital and premotor areas (**hypothesis #4)**; and (4) the relationship of mastery of object permanence to achievement on tests of executive function (the NEPSY) at 6 and 7 years already included within the long-term follow up study of infants enrolled in the Neuroimaging secondary study of the SUPPORT trial (**hypothesis #5)**.

Power analysis: We anticipate that the smallest sample size for the above analyses will be for #5, outcomes at 6 – 7 years. Therefore, for a meaningful power analysis, we considered the post hoc comparison of mean IQ at age 6 – 7 years to attainment of object permanence (a score of 0 or 1 vs. 2 or 3), anticipating a one standard deviation IQ difference (e.g., 70 vs. 85). A sample size of 17 per object permanence score is adequate to detect such a difference with 80% power and alpha = .05. Our preliminary data (Watterberg 2007) indicates that 1/6 of our subjects had object permanence scores of 0, 1 or 2, and the remaining half had a score of 3 (Bayley II). The total sample size required at 6 - 7 year follow up would then be 17 x 6 = 102. This power analysis is also adequate for one standard deviation difference in other executive function measures at 6 – 7 years. We then assumed that the attrition rate for the 6 – 7 year follow

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up could be as high as 50%, requiring at least 204 subjects evaluated at the 18 – 22 month visit.

Sample size/patient recruitment: We had initially planned to collect the object permanence items prospectively on patients enrolled in the neuroimaging ancillary study, since that sample size will be adequate to address all hypotheses. The SUPPORT neuroimaging cohort is estimated to include 400 – 450 survivors with complete MRI and ultrasound data. However, > 70 of the patients have already reached their second birthday, and the form changes may not be ready by January of 2009. Therefore, we propose enrolling all patients in the neuroimaging ancillary study by (1) prospectively collecting object permanence items at the time of the 18 – 22 month visit as soon as the form change can be instituted; and (2) retrieving these items for patients in the neuroimaging ancillary study who have already been seen, if the Bayley scoring sheet has been retained. This will help ensure an appropriate sample size for hypothesis #5 (correlation with 6 – 7 year follow up), regardless of attrition.

Budget: The components of the cost for this ancillary protocol include:

(1) Modification of Bayley data entry: this will require entering three specific items from the Bayley. Cost includes personnel time only.

   a. Per Conra Lacy (Coordinator, UNM), it should require less than 15 minutes/patient to enter these data prospectively. To complete as much of the cohort as possible, sites will be asked to retrieve these three items for those patients enrolled in the neuroimaging secondary only, if the raw data has been retained. Abstracting three items from these charts may add an additional 15 minutes/patient. Budget estimate: 450 patients @15mins

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each = 112 hours of coordinator time. Adding 15 mins for each retrospectively obtained score (for a total of ½ hour for each of those patients), estimated at 100 patients x 15 mins = 25 hours of time, for a total of 137 hours @ $35/hour = $4795.

b. RTI programming: Per Dr. Das, "The re-programming needed for the Bayleys will require changes to the DMS form, report, end of record programming change, batch edit change, programming update to the existing Bayley data table on the Centers computers and adding the new fields to the conversion to SAS process. Since it's only 3 purportedly simple questions to an existing form, it wouldn't take as long as creating a new form or adding something with a complicated skip pattern affecting the rest of the form. I would guess around 12 hours of programming time total. Additional time would be added if any special reports needed to be created for tracking, etc. Also, since non-Support Follow-up kids would likely not be answering these additional questions on the form, we may need two different versions of the NF09A (Bayley III) in the data entry system. That could take a little more programming time to manage."

(2) Data analysis: Per Dr. Das, "As for the statistician effort, given that there are quite a few hypotheses to look at, I would estimate 4 weeks of full time work for data prep, additional cleaning if any, analyses, help with drafting the mansucript(s) and help with responding to journal reviews."

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Center: __ Site No: __ Network No: __ __ __ __ Birth Order: __ Mother's Initials: __ __ __, __ __ Follow-up No.: __ __ __ __

This form should be completed (in addition to the NF09A) for all children enrolled in the SUPPORT neuroimaging ancillary study who have taken the Bayley III exam at the 18 + 4 month visit.

A. Bayley III Information

1. Did the infant demonstrate awareness of object permanence as elicited by a positive response to the following Bayley III Cognitive Scale items?

   a. Item 40? Y N

   b. Item 45? Y N

   c. Item 50? Y N

B. Form Completion

1. Date this form was completed? __ __ / __ __ / __ __ __ __
   Month Day Year

2. Initials of person administering Bayley III exam ___ ___ ___

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From: Sood, Beena
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha
Cc: Bara, Rebecca; Johnson, Mary; KATHLEEN F ABRAMCZYK; Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT - Missing outcomes
Date: Friday, January 09, 2009 10:32:27 AM

Dr Higgins – Please see below for update re the WSU Missing outcomes for SUPPORT.

Thanks
Beena

From: Johnson, Mary
Sent: Monday, December 22, 2008 12:10 PM
To: Sood, Beena
Cc: Shankaran, Seetha
Subject: RE: SUPPORT - Missing outcomes

Hi Beena,
See my notations in the original email below...
Please advise how you'd like me to proceed. I'll be out of the office for a bit to get some lunch and pick up an oximeter from CHM. I should be back here by 2 pm. Otherwise, if it's easier, just email me back!

Thanks
Mary
Mary E. Johnson, BSN
Research Assistant - Neonatology
313-993-7216 (O)
page (b) (6)
mejohnso@med.wayne.edu

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 19, 2008 3:34 PM
To: Shankaran, Seetha; Sood, Beena
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. The trial is coming to an end and we would like to have missing data entered as quickly as possible. Please let us know how you are doing. Thanks for all the hard work and effort!!
Rose

CENTER	NETWORK	ROP_message
		(b) (6) -The patient is within their Fol-up window and final ROP status has not been reported. Baby (b) (6) Her last eye exam was (b) (6) She was last scheduled to be seen r (b) (6) but was a No-Show. She was also scheduled to be seen for Follow up on (b) (6) but mom cancelled. I'll have to call mom to get her scheduled for sometime in January. When I speak with her I'll ask about the eye visits.
		(b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
		(b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. These are the (b) (6) . Two issues here. Insurance did not permit follow up with Dr. Lucas. From what I recall and the notes that were made, mom was advised to make appointments with CHM Eye. Children's Eye has not seen either baby. Becky had been in contact with mom who reported that they had moved out of the immediate area and wouldn't be coming to CHM, however she stated that she did get them in to see an ophthelmalogist closer to where they live. She was asked her to send the exam reports a while ago, but that hasn't happened yet. Becky was going to call mom again to schedule their 18 month visits and pursue the eye exam info as well.
		(b) (6) - 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. (b) (6) Her last exam was on (b) (6) (Zone II, Stage II). She had another appointment scheduled for 7/18 and as of 11/26/08 has not been back to Dr. Lucas.
		(b) (6) - 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. (b) (6) Her last exam was on (b) (6) (Zone III, Stage 0). She too had another appointment scheduled but has been a noe show as of 11/26/08 to Dr. Lucas.
		FU_message
		(b) (6) FU window has closed but NF05 and NF09a have not been completed. Baby (b) (6) Follow Up (b) (6) . She's due for her 18 month follow up but will need to be scheduled for mid January. (Laura Goldsten will be out through the first couple of weeks in January).

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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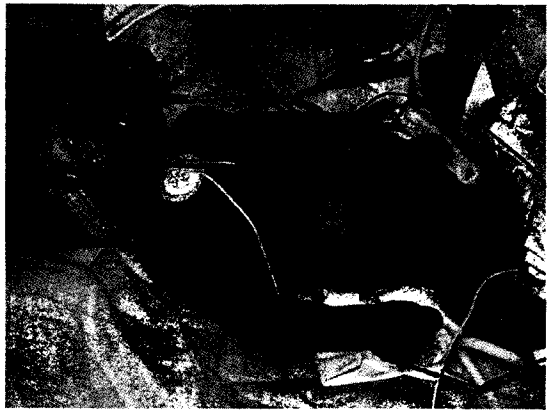
From:	Finer, Neil
To:	Newman, Jamie; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Hammond, Jane; Archer, Stephanie (NIH/NICHD) [E]
Cc:	Zaterka-Baxter, Kristin; Rich, Wade
Subject:	RE: January 5th conference call - Minutes attached
Date:	Friday, January 09, 2009 12:21:41 AM
Attachments:	SUPPORT Progress Jan 09 09.ppt

Hello Jamie and Meg Kris and Rose
This is my presentation for the morning. I believe that I am on around 7:25 PT.
I will call in around 7:15AM PT
Talk to you then
Neil



SUPPORT Progress
Jan 09, 09

Neil Finer

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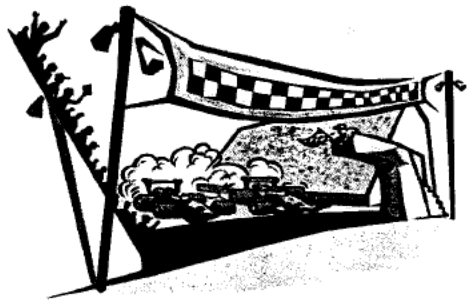
Enrollment



- Currently at 1247 by mid December
- I believe that we will be at 1310 by end February, end March at worst case
- We will discuss closure procedures within the month
- We will then need to have each enrolled infant reach final eye diagnosis etc.
- This could add another 20 weeks - 5 months or more – to August – Sept 2009

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Preparation of Results of First set of Primaries

- We will visit RTI and spend a luxurious week basking in the > 1300 records
- We would then prepare the data, perform analyses, and write the first papers
- I would propose 2 papers – CPAP vs Surf and SpO2 Hi vs Low
- This will be followed by hundreds of subsequent ones!!

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Follow-up

- **Need to follow through initial 18-22 months for other co-primaries**
- **Then to 6 years for extended follow-up for MRI and probably Breathing Outcomes**

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Adverse Events

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.9	10.1	4.4
Air leak (pneumothorax, PIE, pneumopericardium)	9.7(8.2)	12.6 (11)	7.6 (6.1)
Pulmonary hemorrhage	6.7	10.5	4.0
Severe IVH (grades III-IV)	14.4	20.5	10.0

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

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CURPAP Study

- Comparison of prophylactic surfactant

To nCPAP, with early Surf rescue

- Population: 25-28 weeks infants (European multicentre, n=24)
- Outcome:

. Duration of mechanical ventilation during the first 5 days of life

. Mortality, pulmonary and neurological morbidity

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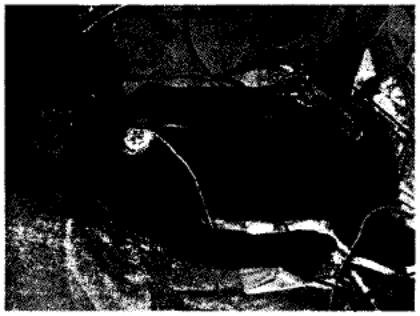

CURPAP Study
Most recently reported

- 103 CPAP vs 105 Prophylactic Surf by 15 min, then extubated by 1 hour
- CPAP failure = Need for intubation, $FiO_2 > 0.40$, $PaCO_2 > 65mmHg$
- 50% of CPAP infants required rescue by 240 minutes (median)
- This is a relatively small study – COIN > 600complete

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CURPAP Study 2008

Parameter	CPAP	Proph Surf
Gestational Age	27	27
Birth weight	913 + 200	967 + 221
Mortality	10.7%	8.6%
CPAP Failure	31%	33%
Pneumothorax	*1%*	*6.7%*
Survived with BPD	22%	23.8%

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Protocol Deviations

- **Protocol Deviations – the commonest are timing issues – failure to give surf within an hour and failure to use the study oximeter when indicated**
- **8 centers with > 30% of enrolled patients with deviations, 2 with over 40%, most related to failure to use Study Oximeter when indicated.**

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Oximeter Downloads

Months	Time on supplemental oxygen	Site	Number of hours	% 88-92	% <84	% 84-96	% >96
Oct08-Dec08	Days of life 1-14	All centers	4261	38.7	7.6	76.3	16.1
Jul08-Sep08	Days of life 1-14	All centers	10895	34.6	9.4	78.9	11.7
Oct08-Dec08	Day 15 to 36 wks	All centers	17707	23.8	13.6	66.5	19.9

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Secondaries MRI

- Update on Neuroimaging secondary enrollment
- a. As of November monthly report – 455 patients with complete neuroimaging including near-term MRI
- b. We will likely have ~500-550 patients with complete neuroimaging by trial close.
- This will be the largest pre-term cohort followed to 6-7 years.

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Neuroimaging

- Tracking tools and reports are now available through the SUPPORT data entry system on Centers' Network computers. The 3-4 year status form will be added to the system soon.
- b. Update on 18-22 month follow-up: As of mid-January 2009, ~100 patients with in Neuroimaging cohort with 18-22 month windows closed
- 91 of these have completed 18-22 month visit; 3 have been
- formally reported as lost to follow-up; 5 not yet seen; 1 reported to be seen at another NRN site

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Other Secondaries

- Growth – 721 enrolled
- Breathing Outcomes - > 700
- Both Breathing Outcomes and SUPPORT – > 400
- Antenatal Consent – 2186 mothers approached, 972 delivered in Window, 1196 consents, 596 enrolled – about 3-4/1

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Summary

- **Please continue with your efforts to enroll in SUPPORT.**
- **We are close to the end, and I believe that in view of the size and design, that this study will probably be the largest of its kind with important therapeutic implications.**
- **Thanks to everyone, especially the coordinators for a tremendous effort!!!**

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From:	Finer, Neil
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	FW: SUPPORT Updates
Date:	Wednesday, January 07, 2009 5:39:29 PM
Attachments:	SUPPORT Enrollment 12-16-08.doc SUPPORT Adverse Events 12-16-08.doc SUPPORT Protocol Deviations - old vs new 12-16-08.doc SUPPORT Protocol Deviations by center - old vs new 12-16-08.doc SUPPORT Use of HFNC 12-16-08.doc All Centers pct in range through Dec08.rtf

Hello Everyone
I will give a brief report at the next Steering Committee this Friday. Attached are the current updates.
1. The enrollment is at 1247 as of Mid December. UI think that we can complete the trial by the end of February as we are 63 short at Mid December and we need 1310
2. The adverse events that we track are below the GDB baseline in both strata apart from air leaks. In this category we are slightly above the GDB baseline 9 12.6 &7.6% vs11% & 6.1%). The European CUROPAP trial was reported at the ESPR and they found a lower air leak rate in their CPAP infants than in the intubated group, but there is as yet no further details for this study.
3. Protocol Deviations – the commonest are timing issues – failure to give surf within an hour and failure to use the study oximeter when indicated
4. Oximeter downloads look the same as our past report. We do better in the first 14 days.
5. The Secondaries especially Breathing Outcomes > 700 enrolled, and MRImaging > 500 enrolled, are going well, with a large number of infants enrolled in both > 400 at last count
6. There will be a 6 year follow-up for the MR study and longer term School Age pulmonary evaluation is also planned – discussed at this meeting
7. Please continue with your efforts to enroll in SUPORT. We are close to the end, and I believe that in view of the size and design, that this study will probably be the largest of its kind with important therapeutic implications.

Thanks to everyone, especially the coordinators for a tremendous effort!!!
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, December 19, 2008 12:19 PM
To: Finer, Neil
Cc: Das, Abhik
Subject: SUPPORT Updates

Neil,

Attached are updates for SUPPORT for the Steering Committee meeting.

Happy holidays!

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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SUPPORT Enrollment as of December 16, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	1247	95%

Enrollment by Center

Center	<Jul-08	Jul-08	Aug-08	Sep-08	Oct-08	Nov-08	Dec-08	Total
3	95	2	2	1	1	0	3	104
4	61	2	2	1	0	0	1	67
5	56	1	4	3	2	1	0	67
8	17	0	0	0	0	0	0	17
9	72	1	5	1	1	4	2	86
11	82	1	1	1	3	2	0	90
12	60	2	2	0	3	0	0	67
13	28	3	1	1	0	1	1	35
14	110	0	0	2	1	7	0	120
15	41	3	2	0	4	2	2	54
16	159	7	2	1	4	2	0	175
18	73	1	1	1	1	2	1	80
19	53	2	1	1	0	1	0	58
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	61	1	3	0	0	1	3	69
23	45	0	0	1	1	2	0	49
24	24	1	0	0	0	0	1	26
25	45	0	1	3	0	0	0	49
26	14	1	0	0	0	2	0	17
Total	1113	28	27	17	21	27	14	1247
Centers		17	17	17	17	17	17	
Avg/center		1.6	1.6	1.0	1.2	1.6	0.8	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	1.9
2.5	1.5
3	1.2

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Percent of SUPPORT infants with selected adverse events as of December 16, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.9	10.1	4.4
Air leak (pneumothorax, PIE, pneumopericardium)	9.7	12.6	7.6
Pulmonary hemorrhage	6.7	10.5	4.0
Severe IVH (grades III-IV)	14.4	20.5	10.0

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak (pneumothorax)	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

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SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	4
Surfactant not given in the first hour (surfactant group)	30
Surfactant not given in the first hour (CPAP group)	36
Oximeter not started within 2 hours	25
Infant received incorrect treatment assignment	16
Failure to use study oximeter at times required by protocol	84
Non-study (unmasked) oximeter used at same time as study oximeter	11
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate CPAP infant if all criteria met	4
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	26
Randomization/consent errors	26
Other	9
Total	293

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	95
Infant received incorrect treatment assignment	16
Failure to use study oximeter at times required by protocol	84
Non-study (unmasked) oximeter used at same time as study oximeter	11
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate infant if all criteria met	5
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	26
Randomization/consent errors	26
Other	9
Total	293

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	0
Surfactant not given in the first hour (surfactant group)	7
Surfactant not given in the first hour (CPAP group)	7
Oximeter not started within 2 hours	7
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	21
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2								1	1									4
Surfactant not given in the first hour (surfactant group)	2	4	2			3	1	3	2	1	3		1					5	3		30
Surfactant not given in the first hour (CPAP group)	4	2	1			3		1	7	3	4	1	11				1	5	2	1	36
Oximeter not started within 2 hours	1	1	2		1	1	2	1		2	2	2	2			1	2	1	4		25
Infant received incorrect treatment assignment	3		1			1	1			2	5		1				1		1		16
Failure to use study oximeter at times required by protocol	3	5	18		2	6	5	1	11	2	7		3				3	6	8	4	84
Non-study (unmasked) oximeter used at same time as study ox.						2	1			1		1	3						3		11
Mechanical ventilation initiated for other than study criteria																	1		1		2
NSIMV initiated in infant not previously intubated	1				1			1			5										8
Extubation (excluding unplanned) for other than study criteria						2			5		2										9
Failure to extubate CPAP infant if all criteria met								1		3											4
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1										2
Infant received postnatal steroids in first 21 days of life	1					2		3	5		3	10	1				1				26
Randomization/consent errors	1	1	4		3	1				4		5	2			1	4				26
Other									3	1	2								2	1	9
Total	16	13	31	0	7	22	10	11	33	19	35	20	14	0	0	2	13	17	24	6	293

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			3%								1%	2%									0%
Surfactant not given in the first hour (surfactant group)	3%	7%	3%			4%	2%	9%	2%	2%	2%		2%					19%	6%		3%
Surfactant not given in the first hour (CPAP group)	5%	4%	1%			4%		3%	7%	6%	3%	2%	2%				2%	19%	4%	6%	4%
Oximeter not started within 2 hours	1%	2%	3%		1%	1%	4%	3%		4%	1%	3%	5%			4%	4%	4%	8%		3%
Infant received incorrect treatment assignment	4%		1%			1%	2%			4%	4%		2%				2%		2%		2%
Failure to use study oximeter at times required by protocol	4%	9%	27%		3%	8%	9%	3%	11%	4%	5%		7%				6%	23%	16%	24%	8%
Non-study (unmasked) oximeter used at same time as study ox						3%	2%			2%		2%	7%						6%		1%
Mechanical ventilation initiated for other than study criteria																	2%		2%		0%
NSIMV initiated in infant not previously intubated	1%				1%			3%			4%										1%
Extubation (excluding unplanned) for other than study criteria						3%			5%		1%										1%
Failure to extubate CPAP infant if all criteria met								3%		6%											0%
Failure to extubate surfactant infant if all criteria met						1%															0%
Infant intubated without meeting study criteria			1%								1%										0%
Infant received postnatal steroids in first 21 days of life	1%					3%		9%	5%		2%	16%	2%				2%				3%
Randomization/consent errors	1%	2%	6%		4%	1%				8%		8%	5%			4%	8%				3%
Other									3%	2%	1%								4%	6%	1%
Total protocol deviations	20%	23%	46%		10%	31%	18%	32%	34%	37%	26%	33%	33%		0%	7%	27%	65%	49%	35%	29%
Total number of infants enrolled	80	57	67	0	73	71	57	34	98	52	137	61	43	0	1	28	49	26	49	17	1000

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0
Surfactant not given in the first hour (surfactant group)	2			1		2	1				1										7
Surfactant not given in the first hour (CPAP group)	4			2												1					7
Oximeter not started within 2 hours						1					5	1									7
Infant received incorrect treatment assignment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1											1	2							4
Other						1					1										2
Total	9	4	0	4	0	7	1	0	4	0	16	2	1	3	3	8	0	0	0	0	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0%
Surfactant not given in the first hour (surfactant group)	8%			6%		11%	10%				3%										3%
Surfactant not given in the first hour (CPAP group)	17%			12%												2%					3%
Oximeter not started within 2 hours						5%					13%	5%									3%
Infant received incorrect treatment assignment	4%			6%							11%					2%					3%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						6%
Non-study (unmasked) oximeter used at same time as study ox															14%						0%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	38%	40%		24%	0%	37%	10%	0%	18%	0%	42%	11%	7%	33%	43%	20%					25%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

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SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of December 16, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			4	5%
4			13	23%
5			10	15%
9			13	18%
11	1	5%	6	8%
12			9	16%
13			5	15%
14	1	5%	6	6%
15			1	2%
16			3	2%
18	1	5%	8	13%
19			9	21%
22			1	4%
23			1	2%
24			1	4%
25			8	16%
Total	3	1%	98	10%

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent [illegible]
Oct08-Dec08	Days of life 1-14	All centers	4261	38.7	7.6	76.3	16.1
		Center 5	802	30.4	4.2	65.4	30.4
		Center 14	712	55.2	5.4	84.9	9.7
		Center 15	579	41.8	9.9	80.7	9.4
	Day 15 to 36 wks	All centers	17707	23.8	13.6	66.5	19.9
		Center 5	4018	28.0	9.2	63.5	27.3
		Center 15	2750	30.9	18.0	70.6	11.3
Jul08-Sep08	Days of life 1-14	All centers	10895	34.6	9.4	78.9	11.7
		Center 3	987	35.2	6.3	77.3	16.4
		Center 4	782	25.7	11.2	74.5	14.2
		Center 5	1060	20.7	8.8	71.1	20.2
		Center 9 site A	1234	37.9	10.8	79.5	9.8
		Center 13	1223	29.7	8.2	82.6	9.2
		Center 16	1778	48.4	9.3	84.7	6.0
	Day 15 to 36 wks	All centers	51905	25.8	13.2	67.2	19.6
		Center 3	4720	26.2	10.1	63.7	26.3
		Center 4	3211	30.4	13.0	70.8	16.1
		Center 5	5497	20.9	11.7	63.3	25.0
		Center 9 site A	3482	27.0	13.4	62.6	24.0
		Center 11	1460	14.8	14.3	54.9	30.8
		Center 12	2597	21.5	9.3	64.4	26.3
		Center 13	3063	20.6	12.4	72.5	15.1
		Center 14	1526	20.3	9.6	63.6	26.8
		Center 15	1783	28.7	15.7	64.5	19.8
		Center 16	7704	31.9	17.5	72.9	9.6
		Center 18	4819	28.5	16.3	67.6	16.1
		Center 25	3231	32.4	11.4	75.6	13.0
Apr08-Jun08	Days of life 1-14	All centers	13939	35.9	9.1	77.3	13.5
		Center 3	951	28.9	9.0	75.0	16.0

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES, THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 4	1139	53.0	2.9	81.5	15.7
		Center 5	1662	28.1	11.4	67.2	21.4
		Center 9 site A	718	48.8	9.4	83.1	7.5
		Center 11	881	16.9	8.8	65.7	25.6
		Center 14	863	37.6	7.3	82.9	9.9
		Center 16	1786	40.3	9.0	81.6	9.3
		Center 18	1052	26.2	7.2	74.4	18.5
		Center 25	1249	54.1	5.6	86.1	8.3
	Day 15 to 36 wks	All centers	60264	30.0	12.7	68.5	18.8
		Center 3	2628	31.1	16.3	67.6	16.2
		Center 4	3717	34.0	9.3	72.1	18.6
		Center 5	4458	24.9	9.9	64.5	25.6
		Center 9 site A	5473	33.5	13.5	71.2	15.3
		Center 11	2968	17.3	9.0	56.7	34.3
		Center 14	6557	36.0	9.0	70.9	20.1
		Center 15	3818	29.5	17.5	72.5	10.0
		Center 16	7841	33.6	12.0	75.5	12.5
		Center 18	1977	25.4	14.4	64.1	21.5
		Center 24	3433	19.5	22.4	56.7	20.9
		Center 25	9069	35.8	10.3	69.0	20.7
Jan08-Mar08	Days of life 1-14	All centers	9388	35.6	9.3	78.7	12.0
		Center 3	1241	38.6	8.9	78.3	12.9
		Center 5	829	23.5	7.7	66.4	25.9
		Center 11	901	24.7	10.2	76.9	13.0
		Center 14	591	51.6	4.7	83.5	11.7
		Center 16	1499	37.7	10.9	83.0	6.1
		Center 25	1064	51.7	4.2	85.4	10.3
	Day 15 to 36 wks	All centers	35919	27.8	14.2	67.2	18.6
		Center 3	4965	26.5	19.8	67.9	12.3
		Center 5	3691	28.3	11.8	66.1	22.1
		Center 11	2549	16.4	8.3	60.6	31.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES, THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 12	3255	37.2	11.0	68.5	20.5
		Center 14	1807	29.9	11.5	69.3	19.3
		Center 16	6947	29.0	15.7	72.4	11.8
		Center 18	4199	29.6	17.6	68.7	13.7
		Center 19	726	20.2	3.1	39.8	57.2
		Center 24	2859	23.7	15.1	63.9	21.0
		Center 25	924	26.1	8.8	79.3	11.9
Oct07-Dec07	Days of life 1-14	All centers	9501	31.5	9.2	76.9	13.9
		Center 3	1307	35.6	8.5	77.5	14.0
		Center 5	1741	32.6	7.7	70.9	21.4
		Center 16	2182	42.1	9.8	84.1	6.0
	Day 15 to 36 wks	All centers	44897	25.6	12.9	65.8	21.3
		Center 3	4597	33.0	14.2	69.4	16.4
		Center 5	8024	23.3	10.4	61.3	28.3
		Center 11	1138	24.6	10.2	54.4	35.4
		Center 12	1573	28.6	7.1	63.9	29.0
		Center 14	1386	20.9	13.3	63.9	22.8
		Center 15	2869	23.6	17.7	64.7	17.5
		Center 16	7237	26.1	14.6	70.7	14.7
		Center 18	1585	26.0	15.7	72.9	11.5
		Center 23	2680	28.8	10.8	61.4	27.8
		Center 25	6171	24.5	9.6	73.3	17.1
Jul07-Sep07	Days of life 1-14	All centers	15295	34.2	7.4	76.3	16.3
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1404	34.6	9.6	74.6	15.8
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9
		Center 16	1173	39.5	7.4	81.3	11.3
		Center 23	2150	32.6	5.5	71.6	23.0

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 25	2158	40.4	5.5	83.9	10.6
	Day 15 to 36 wks	All centers	56270	25.6	11.3	65.9	22.8
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5761	21.0	9.5	59.7	30.8
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	15479	34.1	9.0	76.5	14.5
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1062	31.1	11.5	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1439	40.3	8.5	85.7	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	1127	18.3	6.9	69.7	23.4
	Day 15 to 36 wks	All centers	56188	28.5	12.2	66.0	21.9
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		. .....	4086	23.7	10.1	57.7	32.2

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Sites	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	4710	29.9	13.1	69.8	17.1
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2857	22.4	9.4	55.4	35.2
Jan07-Mar07	Days of life 1-14	All centers	16863	35.4	8.3	78.0	13.6
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	54920	27.9	12.5	68.9	18.6
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8
		Center 16	3347	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES, THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	4307	20.2	17.7	64.5	17.8
Mar06-Dec06	Days of life 1-14	All centers	33182	37.3	8.1	79.1	12.8
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2456	33.1	9.1	67.8	23.1
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5671	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	881	30.5	6.0	77.5	16.6
		Center 25	1477	49.5	5.8	84.3	9.9
	Day 15 to 36 wks	All centers	107540	29.2	12.5	68.3	19.1
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3278	29.7	11.8	72.9	15.3
		Center 11	6552	28.9	10.3	61.6	28.1
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14378	29.3	12.5	69.1	18.4
		Center 18	14879	24.1	17.0	66.3	16.8
		Center 19	1695	24.5	7.9	56.8	35.3
		Center 25	6484	39.9	9.3	77.0	13.7
Through Feb06	Days of life 1-14	All centers	27099	38.1	9.3	79.6	11.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1448	32.0	10.0	77.5	12.5
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1517	42.1	9.5	85.5	5.0
		Center 22	3586	40.3	8.6	80.1	11.3
	Day 15 to 36 wks	All centers	133420	26.5	12.2	67.6	20.2
		Center 3	13570	17.7	17.4	64.2	18.4
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	5473	19.1	9.2	58.6	32.1
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	8688	28.1	17.8	63.6	18.6
		Center 19	1280	35.4	7.7	77.5	14.9
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	3563	29.6	16.7	68.7	14.6
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Betty Vohr
Subject: RE:
Date: Tuesday, January 06, 2009 6:21:12 PM

Rose and Betty,

Some thoughts about the discrepancy between 2004-5 and 2006 ELBW NDIs:

Since there is no reason for actual outcome to have changed dramatically over this time period, the much lower frequency of NDI reflects changes in test instruments and NDI definition used.....specifically the development criteria as the other components (neurologic, vision, hearing) have remained unchanged. It is not surprising that the Bayley-III cognitive scores are higher than the Bayley II MDI since language tasks and some fine motor tasks such as stacking blocks (areas in which our ELBW children are often delayed) are no longer included in the cognitive score. (Also, per Martha, a few items such as the yellow pegboard series seem to be more generously scored on the Bayley III compared to the Bayley II.I don't know if others have this same impression.) As a result fewer children will have cognitive scores < 70 which is now the only independent determinant of development disability. (The GMFCS ³2 is already used as the determinant for neurologic disability and is thus adding no new information to the developmental component.) It would be interesting to see what proportion of children had a PDI <70 which includes both fine and gross motor skills and a GMFCS < 2 which would have qualified them as NDI in 2004-5 but not in 2006.

Would combining the Bayley III cognitive and language scores result in a score closer to the Bayley-II MDI used previously? If so, perhaps we could use that composite cognitive-language score and moderate-severe CP (excluding the PDI) to define NDI more comparably between the two time periods. The 2006 NDI definition using cognitive < 70 or moderate-severe CP may be more predictive for future disability since motor delays unrelated to moderate-severe CP improve over time as does language function.

Since the incidence of NDI is so important in influencing counseling and medical support for the ELBW, it is important that we use a NDI definition yielding the most accurate prediction of longterm disability.

Yvonne

PS Happy New Year!

Yvonne E. Vaucher, M.D., M.P.H.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 18, 2008 10:00 AM
To: apappas@med.wayne.edu; EMcGowan@tufts-nemc.org; Acarregui, Michael; adusick@iupui.edu; Betty_Vohr@brown.edu; cbauer@peds.med.miami.edu; (b) (6) Gary_myers@URMC.Rochester.edu; golds005@mc.duke.edu; Ira Adams-Chapman;

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Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Jamie Newman; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Ed Bell; Ed Donovan; Ivan Frantz; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); VanMeurs, Krisa

Subject:

Hi,

Attached is a Bayley score comparison from 2004-2006 – the 2006 year uses the new definition for cognitive score and the number of children with NDI is significantly reduced. Implications for this with ongoing studies and planned will be discussed on the Steering Committee PI call next week. Your input is needed. It would be helpful for site PI's to get thoughts from the FU PI's prior to the call, if possible.

Thanks

Rose

Rosemary D. Higgins, MD
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From: Frantz, Ivan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Enrollment question
Date: Monday, January 05, 2009 9:24:55 PM

Thanks. See you Thurs.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 1/5/2009 12:40 PM
To: Mackinnon, Brenda
Cc: Frantz, Ivan; Archer, Stephanie (NIH/NICHD) [E]; Poe, Grace (NIH/NICHD) [E]
Subject: RE: SUPPORT Enrollment question

Brenda and Ivan,
You have our permission to continue to recruit patients into SUPPORT until the trial is finished. We are very close to completing recruitment, but want all eligible study subjects to continue to be approached for consent.

Thanks
Rose

From: Mackinnon, Brenda [mailto:bmackinnon@tuftsmedicalcenter.org]
Sent: Monday, January 05, 2009 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Frantz, Ivan
Subject: SUPPORT Enrollment question

Hi Rose,
I am writing as Ivan had to leave town emergently. We have now enrolled 53 babies into the SUPPORT trial. When we reached our number previously we were allowed to use INS1 funds to continue enrolling up to 55 infants in SUPPORT. Now that we are so close to the 55 I was wondering once we hit 55 are we done enrolling or are we to continue until the overall number is reached? I need to know so when I leave for the meeting I have a plan in place for those left back in Boston who will be covering the study.
Thank you,
Brenda

Brenda MacKinnon, RNC NRN Coordinator
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